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## Thrombo-angiitis obliterans

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THROMBO-ANGIITIS OBLITERANS

A Review of the Literature

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## I N T R O D U C T I O N

Until comparatively recently, the study of thrombo-angiitis obliterans had occupied the step-child's seat in the medical household. However, probably concomitant with - or symptomatic of - recent developments in diagnosis and therapy, there has been an up-swing in regard to interest in this branch of medicine. It seems that interest and progress in this field is due for a period of further augmentation and thus furnishes the *raison d'etre* of this particular thesis. It is felt that when the threshold of accelerated development is entered upon, it is very necessary to have a comprehensive understanding of what has gone before. With this in mind an attempt has been made, not only to define the present-day status of this study, but further, to trace the initiation and development of modern ideas from the perhaps misty days of their inception. There will be seen abortive efforts, perhaps widely acclaimed at first, but which slowly (or rapidly) sank to oblivion; some ideas may seem patently absurd. However, they will be presented, not as targets for ridicule or objects of fatuous tolerance, but as examples of previous sincere work which failed to materialize. An attempt will be made to define present status in the various divisions and evaluation will be essayed, mostly on the

basis of comment in the literature; the author realizes his youth in point of medical experience and is hardly sufficiently presumptive to attempt to criticize or evaluate in his own right. Emphasis will be placed upon the consideration of therapy, not only because of the obvious pragmatic reason, but also because it apparently offers the most fertile field for future investigation.

## HISTORICAL

In modern discussions of thrombo-angiitis obliterans, brief and quite glib mention is made to the effect that the disease was correctly and comprehensively described by Buerger in 1908. No word is given of the intrepid and greatly handicapped workers, who, as much as two hundred years ago, hinted at the first glimmerings of what is now seen as light.

As early as 1739, Quesney hinted that peripheral gangrene might be due to organic occlusion of the arteries. This was reiterated almost one hundred years later, by Hebreard, and by Avisard — 1817 and 1819, respectively. However, these works were backed by no actual proof and lack of corroboration consigned them to limbo.

The French continued in their representation of those prominent in the disease; Dupuytren and Roche were the first to postulate the basis of arterial inflammation for occlusive arterial lesions. Raynaud, in 1862, whose famous thesis has received well-earned recognition ("On Local Asphyxia and Gangrene of the Extremities") proved the then-startling fact that gangrene can be produced in arterial affections without the existence of arterial occlusion. This refers, of course, to the disease that now bears his name.

The first report of what is now known as thrombo-angiitis obliterans is believed to have been presented by Von Winiwarter in



1879. Fourteen years had to elapse before 1893, when another case was presented; in reporting this case, Dutil and Lamy emphasized the cardinal points of intermittent claudication, absent pulses, coldness, and gangrene.

In 1898, Wwedensky reported on the incidence of the disease in those parts of Russia which were subject to very cold weather. He added to previous observations that cold weather seemed to cause intensification of the symptomatology. No mention was made of any association with ergotism.

Until 1908, when Buerger wrote his first paper, the disease was known by a wide variety of names, which, if naught else, serves to illustrate the then-existing confusion. Some of these names follow: Presenile gangrene, spontaneous gangrene, local asphyxia of the extremities, acroasphyxia, acrocyanosis, non-syphilitis endarteritis of Jews, Russian disease, Jewish disease, Yiddish disease, Raynaud's disease, scleroderma, Friedlander's disease, gangstockung, dysbasia angiosclerotica, erythromelalgia.

In 1908, when Buerger, of Mt. Sinai Hospital (New York) wrote his first paper and gave a detailed consideration of pathology and symptomatology, he suggested the use of the descriptive name of "Thrombo-angiitis Obliterans". This, apparently by virtue of apt word-summary, has become widely accepted.

Almost twenty years later, Buerger came forth with his latest great contribution to the knowledge of the disease (1924). In this

significant volume ("Circulatory Disturbances of the Extremities", Saunders and Co., Philadelphia, 1924) he gave not only a detailed discussion of thrombo-angiitis obliterans, but also considered at length the other conditions comprising peripheral vascular disease.

With these brief prefative remarks, we now approach the consideration of the first section.

## E T I O L O G Y

The etiology of thrombo-angiitis obliterans is, as yet, essentially unknown. Medical text-books, until comparatively recently, had disposed summarily of this phase of the subject in a single sentence: "Thrombo-angiitis obliterans is a disease that occurs in young Jewish cigarette-smoking males of Russian and Polish origin." In the following, it will be attempted to enlarge upon and add to the five etiological factors concisely mentioned in the quoted sentence:

### 1. AGE

Thrombo-angiitis obliterans is a disease that is characteristically found in young or early middle-aged individuals. Thus, it is generally agreed that the limits of incidence lie almost constantly between the ages of twenty-five and fifty years. This is the figure arrived at by E.V. Allen and G.E. Brown (12), who, in 1928 summarized the existing literature and submitted their own series of two hundred cases. In their series, one hundred and forty-four cases of the two hundred showed an age incidence of twenty-five to fifty years, or seventy-two per cent. The cases outside the given limits of incidence did not significantly affect the statistical figure, for there was seldom a variance of more than five years. Occasionally, of course, a striking case will show at an age much removed from the usual figure,

as in the case reported by J.A. Cahill, Jr. (12-A) in which the patient was two years of age. Buerger (8) mentioned the possibility of, and actual occurrence, of the disease in very young individuals.

The question arises, "Why should the disease be found in a given age incidence rather than dispersed more widely?" It is impossible to answer this question with accuracy and universal acceptance of opinion, for the basic etiology is still undetermined, and many opinions are to be proved or disproved. Those who hold that tobacco intoxication is the basic etiology will postulate that a certain time must elapse after the individual starts to smoke before the effect of the intoxication becomes apparent. The investigators who subscribe to the hereditary nature of the disease would probably hold that the disease, by virtue of its hereditary nature, tends to appear at a given age, as perhaps in the manner of Huntington's Chorea. These are merely two obvious examples of influence of the basic etiology upon the age incidence. Other examples will become apparent as the elucidation of the various theories of etiology proceeds.

In conclusion of the question of age incidence, it may be stated that the vast majority of cases will be found between the ages of twenty-five and fifty years. It is perhaps of significance that at the Mount Sinai Clinic, when the diagnosis is uncertain, and all other considerations are equal, those cases under forty-five years are considered thrombo-angiitis obliterans, while those beyond that age are considered arteriosclerosis - in the sense, to be sure, of a working diagnosis.

## 2. RACE

From a time very early in the history of the knowledge of the disease, the apparent association with the Jewish race had been discerned. This is borne out by certain of the earlier names given to the disease -- names such as "Russian Jewish disease", "Yiddish disease", "Non-syphilitic endart<sup>is</sup> of Jews." Further impetus to the racial conception of the disease was given by the work of Buerger (8), who found that "about ninety-nine per cent of cases were Polish, Galician, or Russian Jews." However, since Buerger's work had been published, proper evaluation thereof reduced the significance of his observations in regard to this factor. It was pointed out that his work was done at Mount Sinai Hospital, (New York), at which institution the clientele is almost exclusively Jewish. It is obvious, then, that his finding the disease almost invariably associated with the Jewish race rests, to a large extent, on the fact that he was not dealing with a group representative of the population at large.

E.V. Allen and G.E. Brown (12), in their series of two hundred cases, report<sup>ed</sup> that fifty per cent of cases were Jewish; the rest of their cases included almost world-wide representation, showing Austrians, Finns, Norwegians, Germans, Scotch, Irish, French, English, Dutch, Greeks, native Americans and those of mixed ancestry.

The disease was reported in Chinese by Meleney and Miller, in Japanese by Koyano and Ito (6), in Koreans by Ludlow (20), in Turks

by Wieting, and a questionable case in a negro was reported by Gemmill (9).

In an early publication Willy Meyer (35) saws the question of race as a definite predisposing factor. He felt that the etiology of thrombo-angiitis is two-fold:

- "(a) A sub-normal hyper-excitable type of nervous system, a sort of neurasthenia — found in Hebrews, especially those of Polish-Russian descent, who are subject to much persecution.
- (b) The effect of substances taken into the body in excessive cigarette smoking."

It is seen that this theory depends upon the questionable basis of hereditary functional nervous disease in a specific instance, and thus lies open to reasonable doubt.

However, Meyer's theory may be construed as gaining in weight from the material reported in a very recent publication. Last year, 1936, Maddock, Malcolm, and Collier (52) found that cigarette smoking by Jewish males caused a greater drop in the skin temperatures of their fingers and toes than occurred in Gentile males.

In summarizing the etiological role of race, it must be stated that, while it does not play so large a part as originally believed, it apparently does have some influence. Just why those of the Jewish race are apparently more susceptible to thrombo-angiitis obliterans has not, as yet, been shown satisfactorily.

### 3. TOBACCO

The fact that the use of tobacco is found in the vast majority of thrombo-angiitis obliterans patients has repeatedly been pointed out by innumerable workers in this field. These observations gave rise to the formulation of an etiological role in regard to the habit.

Willy Meyer (5) considered excessive cigarette smoking as the precipitating agent for his postulated hyper-excit<sup>ed</sup> nervous system.

In their series, Allen and Brown (12) found that only three patients out of two hundred were total abstainers. In a control series of patients with other diseases, but comparable in age and sex, forty were total abstainers. The authors, however, warn<sup>ed</sup> against jumping to apparently obvious conclusions, pointing out that smoking may have been taken up after the condition (thrombo-angiitis obliterans) had developed, because of the pain and worry. They felt free to conclude, however, that "...Smoking is more common in thrombo-angiitis obliterans patients, and may constitute a contributing etiological factor."

However, Barker (19) found from a study of three hundred and fifty cases that tobacco wasn't necessarily an etiological factor, pointing out the occurrence of thrombo-angiitis obliterans in patients who never consumed tobacco. Barker did admit, however, that in his series, the use of tobacco definitely increased the severity of the disease.

About four years ago Harkavy, Hebold and Silbert (28) pointed out "In the large experience of Silbert, no typical instances of thrombo-angiitis obliterans have ever been observed in non-smokers", and "Silbert has noted clinically that cessation in the use of tobacco has often definitely arrested the progress of the disease." It may be pointed out that this latter observation loses significance because of the fact that thrombo-angiitis obliterans is often characterized by spontaneous remissions. However, a certain amount of weight must be attached to it, if for no other reason than because such large numbers of patients are followed up at the large clinic in question.

Maddock and Collier (32) found that the smoking of tobacco causes:

- (1) Decreased skin temperature.
- (2) Increased pulse rate.
- (3) Increased blood pressure.

This was found both in normals and in thrombo-angiitis patients. Analogous results were obtained from the intravenous injection of nicotine (weight theoretically similar to that obtained by the smoker from two cigarettes -- 3.33 mg. per cigarette). This effect on skin temperature was found to be apparently on the basis of stimulation of sympathetic system by tobacco products. The authors did not say that tobacco is the etiological factor in thrombo-angiitis obliterans, but pointed out that it may play a role such as ergot and pituitrin, and



that constriction on a fundamentally neurological basis may later result in organic vascular occlusion.

The contention of Maddock and Collier that tobacco smoking results in vasoconstriction found adequate substantiation in (39) in which Johnson and Short reported that in their series of experiments, skin temperature was definitely decreased. In the same publication, the work of Simici and Marco, and of Bruce, Miller and Hooker is reported. All results substantiate the indicated conclusion.

More recently, Lampson (42) not only studied the effect of tobacco per se, but he sought to inquire into the variations dependent, possibly, upon different types of tobacco consumption. He found that the inhaling of one cigarette's smoke caused a sudden marked vasoconstriction which lasted for about sixty minutes. The possible importance of this single observation may perhaps be emphasized by pointing out that many thrombo-angiitis obliterans patients give a history of having consumed forty to sixty cigarettes daily over periods of years. If one cigarette can cause a one-hour's vasoconstriction, these patients apparently must have had a continual state of spasm in their vessels. Further, the significance of this must be considered in the light of the speculation of Maddock and Collier (32) that vessel spasm may result in organic occlusion.

Lampson found also that the matter of inhaling was apparently of some importance -- for cigarettes which were smoked, but not inhaled, produced a vasoconstriction reaction which lasted for fifteen minutes.

Cigar and pipe smoking induced a similar vasoconstriction - and a similar variation in regard to the matter of inhaling.

The last of Lampson's observations may have a bearing on Willy Meyer's theory of tobacco acting on a hyper-irritable nervous system. Lampson found that thrombo-angiitis obliterans patients responded to tobacco consumption in the same manner as normal subjects.

It will be observed that the fore-going material has dealt with the role of tobacco in thrombo-angiitis obliterans by a manner of inference -- in certain of the cases postulating a nervous mechanism for the vascular phenomenon that may be responsible. There have been no cases of controlled tobacco consumption resulting in disease. While this is obviously not feasible in humans, work has been done on animals.

Less than one year ago Friedlander, Silbert and Laskey (49) subjected rats to the administration of tobacco through various routes. Intraperitoneal injections were made in forty-eight male rats and in twelve female rats. Thirty-three male rats developed gangrene of the toes in five to twelve weeks; none of the female rats treated for five to eighteen weeks developed this lesion. In ten control males, under identical conditions, no gangrene developed. Of six rats subjected daily to inhalation of tobacco smoke, over a period of five months, one male animal developed lesions exactly like those produced by injections of tobacco extract.

While it must be remembered that <sup>the</sup> results of animal experimentation are not necessarily applicable to human disease, this work presents

a possibly significant sign-post in the road to a final truth.

Silbert, at the Mount Sinai (New York) Clinic, is convinced of the importance of smoking in thrombo-angiitis obliterans. He says unequivocally, (41):

"I know that in taking the stand that thrombo-angiitis obliterans never occurs except in those who smoke, I am not in complete agreement with other observers. My explanation of this difference of opinion is that those who report thrombo-angiitis obliterans in non-smokers are not careful to exclude other forms of vascular disease, particularly true, pre-senile arteriosclerosis."

Certain investigators have looked to the phenomenon of the allergic response in the quest for information as to the etiological role of tobacco. Harkavy, Hebald, and Silbert (28) feel that it is "...Clearly demonstrated that a large percentage of patients suffering from thrombo-angiitis obliterans belong to the category of allergic individuals, and that this allergy is essentially characterized by a hyper-sensitiveness to tobacco." In 1934, Harkavy (34) found that in normal smokers there was no allergic response to tobacco pollen or seeds without concomitant reaction to ragweed or timothy. This was interpreted as indicating that the reaction to tobacco is a manifestation of a general allergic response (multiple sensitization.) It was found that, in thrombo-angiitis obliterans patients, reactions to tobacco pollen and seed, while lower than those to the leaf, approximate them, while occurring six times as frequently as skin reactions to ragweed and timothy. In the same year, it was found, significantly, that there was a strikingly larger number of positive skin tests to

tobacco in thrombo-angiitis obliterans cases (sixty-nine per cent) as compared <sup>with</sup> ~~to~~ the skin tests in controls (eleven per cent).

In concluding a review of the etiological role of tobacco, certain facts may be considered as true:

- (1) The association of thrombo-angiitis obliterans and the use of tobacco has been practically universally noted.
- (2) Tobacco consumption as the basic etiology is not generally accepted, but is not necessarily ruled out.
- (3) There is widespread acceptance of tobacco consumption as an important contributory factor in etiology; this factor seems to be based on the production of a vasoconstriction.
- (4) Recent work indicates that the etiological role of tobacco may be on an allergic basis.

#### 4. SEX AND POSSIBLY RELATED FACTORS

It had been long held that thrombo-angiitis obliterans is limited to the male. However, cases have been reported in which the patient was female. Telford and Stopford (11) reported two cases of the disease in women. Other cases of thrombo-angiitis obliterans in the female were reported by Koyano (6), Meleney and Miller, Buerger (8), Silbert (41) and by Herrell and Allen (51). There were no females in the two hundred cases reported by Brown and Allen (12). It seems, therefore, that although the premise that the disease is limited to the male is wrong, it must be admitted that the incidence in females is significantly low.

Various suggestions have been offered, and not a little work

done, in a quest for the reason for the discrepancy in sex incidence.

One possible explanation is that of an endocrine basis. Koyano of Japan, in his study of one hundred and twenty cases (6) noted an increase in blood viscosity. This is possibly related to the finding by Silbert and Friedlander (21) that the blood volume in thrombo-angiitis obliterans patients is less than in the normal individual. The latter investigators administered thyroid extract to the thrombo-angiitis obliterans patients and found the blood volume to be definitely increased. This increase, however, was temporary and gradually fell during continued thyroid administration. Cessation of thyroid administration was followed by a prompt return to the original blood volume figure. They found that the blood chemistry underwent simultaneous changes, so that the figures for total protein, cholesterol and calcium were diminished to normal during the thyroid administration, but returned to the original figures on withdrawal of the thyroid. In further work on the blood chemistry, Silbert and Friedlander (22) confirmed the fact that in thrombo-angiitis obliterans there is concentration of the blood, and increase in the figures for total ash content, cholesterol, calcium, and total protein. They point<sup>ed</sup> out that this may be interpreted as a relative increase, caused by the lowered blood volume, but doubt<sup>ed</sup> that such objection holds, since, while the indicated figures increase, that for phosphorus content decreases. It should be mentioned that Silbert and Friedlander (21) had found the basal metabolism to be lower in thrombo-angiitis obliterans patients and in male smokers. This work points to a possible factor to be considered. Another follows.

In 1933, Friedlander, Laskey and Silbert (31) made a study of women who had undergone bilateral oophorectomy. In these individuals the blood volume was reduced to about twenty-five per cent of normal. In patients who had had a natural or artificial menopause (but no bilateral oophorectomy) the blood volume was found to be within normal limits. From their results the investigators infer:

"Therefore, it seems that some factor influencing blood volume is produced by the ovary, even after other physiological functions have ceased."

In further work along this same line, the same investigators (46) again reported<sup>ed</sup> reduction of blood volume in patients that had undergone bilateral oophorectomy; the blood cholesterol, fibrinogen, and viscosity underwent a coincidental increase. Similar changes were found in a series of female cats subjected to bilateral oophorectomy, while in a control group of eleven patients who had undergone natural or artificial menopause (but no bilateral oophorectomy), there were no changes in blood volume or chemistry. This study suggested:

- " 1. Possible importance of the ovaries as a protective mechanism against the disease.
2. Reduced blood volume may precede the development of the disease. "

In 1935 Silbert reported two cases in women (41), and at this time stated:

"Evidence is as yet inconclusive, the striking limitation of thrombo-angiitis obliterans to the male sex and the great preponderance of cases in

the Hebrew race suggests that there is a sex-linked hereditary factor in this disease."

He pointed<sup>d</sup> out the possibility that thrombo-angiitis obliterans may be a sex-linked disease (in the manner of hemophilia) but through some variation, there may be cases in which it may affect the female who would ordinarily only transmit it to the future male.

McGrath (45) again focused attention upon a possible protective mechanism resident in the ovary. He produced gangrene in the tails of female rats by the administration of ergotamine tartrate. If theelin were injected into these rats, the same amounts of ergotamine did not cause gangrene. Theelin did not, however, protect male rats from ergotamine-induced gangrene.

Theories, other than those on endocrine bases, have been evolved to explain the variation in sex incidence of the disease. Horton and Brown (25) present<sup>ed</sup> ten cases of thrombo-angiitis obliterans in the female, and, while admitting that the disease is much rarer in the female, postulate<sup>d</sup> that women do have the disease. They postulate<sup>d</sup> that, while women are subject to the disease, theirs is a much milder form, so that it is usually overlooked, inasmuch as it seldom causes serious sequelae.

Others postulate<sup>d</sup> that the disease really has no variation as regards sex incidence. They claim<sup>ed</sup> that the reason more cases are not seen in women is because women do not smoke as much as men. Maddock, Malcolm, and Collier (52) showed that cigarette smoking in women resulted in a drop in skin temperature, and increased pulse and blood pressure, similar to that produced in men. For evaluation

of this theory, it seems we shall have to wait until such a time when women will have equalled men in the matter of tobacco consumption -- a time, apparently, not very far in the future.

It is to be seen, then, that the disease, although rarer in females at this time, is definitely found in that sex. Definite explanation for this phenomenon is, as yet, not known.

#### 5. INFECTION

From a time early in the history of the disease, various investigators have postulated the existence of an etiological basis of infectious nature.

Buerger himself, from his study of the histopathology, definitely felt that activity indicative of a microbial agent was indicated.

Slightly more than twenty years ago, the idea was advanced that latent typhus was the basic cause of thrombo-angiitis obliterans (Goodman and Bernstein (1) ). This series, however, was not well substantiated; only three of the twenty-one cases showed positive serology for typhus. In September, 1916, Professor Bruno Wolff stated that gangrene of the extremities was among the most frequent clinical manifestations of typhus (quoted in 13). Goodman's thesis is further based (2) on the work of Fraenkel, who concluded that the areas of necrosis shown in arterial walls after typhus must be considered pathognomonic of the disease. In Fraenkel's opinion, this was not seen more often because it required for demonstration a difficult,



special technic. For almost twenty years, there had been apparently very little work on the matter of typhus in thrombo-angiitis obliterans. Then, in 1935, Goodman and Brodie (43) were again heard from. They presented a series of fourteen cases of thrombo-angiitis obliterans and twelve controls. Skin tests for typhus were performed on all the individuals, and it was found that all the thrombo-angiitis obliterans cases reacted positively. Reaction in any of the controls was negative or, at best, doubtful. This work has not been corroborated. The work on the etiological role of typhus has been quite scanty, and further consideration of this factor must necessarily await additional investigation.

In 1925, Rabinowitz (7) claimed to have isolated an etiological organism. From a culture of pathological vessels, he obtained a gram negative bacillus of the following characteristics: Aerobic, facultative anaerobic, freely motile, 0.5 to 1.0 microns in diameter and 0.5 to 1.0 microns in length (sic). No capsule, spores, or flagellae were seen. Best growth obtained on Loeffler's medium. There occurred fermentation of glucose, saccharose, and mannitol, but not of lactose. Indol reaction on sugar-free broth was negative. On agar, colonies were scanty, raised, and smooth, rather translucent, colorless, round, with a sharp border. Best growth at thirty-seven degrees Centigrade, maximum temperature fifty degrees Centigrade, minimum twenty degrees Centigrade. When this organism was injected into rabbits, lesions were found which were similar to those of thrombo-angiitis obliterans in gross and microscopic pathology. The organism was recovered from

the experimental animal. Unfortunately, this interesting work received no corroboration.

In 1930, Horton and Dorsey (15), of the Mayo Clinic, obtained in pure culture from acutely inflamed arteries and veins of nine thrombo-angiitis obliterans cases of thirty-four, a gram positive pleomorphic streptococcus, and from two of the thirty-four cases a green-producing streptococcus. Negative cultures were obtained from twenty-four of the thirty-four cases of the series. The organisms were introduced, by various routes, into the bodies of rabbits and dogs; lesions similar to, or identical with, those of thrombo-angiitis obliterans were found in twenty-five per cent of the experimental animals. Rosenow stated that he never saw these lesions develop spontaneously in rabbits, but added that, inasmuch as the experiment had not been adequately controlled, the result could not be taken as conclusive. G.E. Brown, of the same institution, added that this research was interesting, but not conclusive, and suggested that further experiments be done with normal and arteriosclerotic tissues. Two years later, Horton and Dorsey (26) presented another series, in which they isolated a similar organism and succeeded in apparently producing thrombo-angiitis-obliterans-like lesions in a minority of experimental animals. Inasmuch as corroboration of this investigation has not appeared, acceptance of its veracity must be kept in abeyance.

In 1928, Allen and Brown (12) suggested the possible role of focal infection. In their series of two hundred cases, seventy-five

per cent had clinically important dental infection, eighty per cent had infected tonsils. One-fourth of the cases had prostatic examination; of these, fifty-two per cent had prostatitis of clinical importance. In only three cases of the series there was no evidence of demonstrable foci of infection. The literature is lacking in further work on this phase.

It had been suggested that syphilis had etiological significance in thrombo-angiitis obliterans. Smith and Petterson (10) presented a case in a known luetic and advanced the spirochaetal infection as the basis for the vascular pathology. Many investigators pointed out subsequently that lues may be found coincidentally; in the two hundred cases of Allen and Brown (12) only three cases had positive serology. It is quite widely held that syphilis plays no part in the causation of thrombo-angiitis obliterans; when the two conditions are found together, it is regarded only as a matter of association.

In October, 1936, Allen and Lauderdale (53) presented the case of thrombo-angiitis obliterans in a surgeon. This surgeon had wounded his fingers in removing a toe in a case of thrombo-angiitis obliterans; thrombo-angiitis obliterans subsequently developed in the involved fingers. The authors, in pointing out the possible infectious basis, indicate<sup>d</sup> the work of Schmidt-Weyland. This worker found that intravenous injection of streptococci of high virulence, tubercle bacilli of human and bovine strains, and killed colon bacilli, produced gangrene in twenty of forty-eight experiments, provided that 0.5 c.c.

of a 1 - 1000 solution of epinephrine chloride was injected near the base of the rabbits' ears daily. Control experiments consisting of similar injections of tubercle bacilli, streptococci, and colon bacilli, and of epinephrine separately, did not produce gangrene. This work suggest<sup>ed</sup> that bacteria, aided by a vasoconstriction mechanism, may be responsible for the production of the lesions of thrombo-angiitis obliterans. It is obvious, however, that application of these results to the disease in man would be premature and ill-advised.

In regard to the infectious theory of etiology, it seems that, although suggestive work has been put forth, serious acceptance must be withheld for want of adequate confirmation.

#### 6. ERGOT

The origin of ergot in contaminated rye and its potent vasoconstrictive action has long been known. Many cases of gangrene due to ergotism had been seen in Southeastern Europe. In 1932, Klein (23) postulated that ergot intoxication may be the essential or contributory etiology of thrombo-angiitis obliterans. He pointed out a series of cases of what was apparently ergotism among the Jewish population of Manchester, England. This series was believed due to the ingestion of rye bread made from contaminated grain.

In the same year, Kaunitz (27) point<sup>ed</sup> out the danger of eating grains contaminated with ergot. He further point<sup>ed</sup> out that the pathology in ergotism and in thrombo-angiitis obliterans are, in certain respects, quite similar. On this basis, he suggest<sup>ed</sup> the possibility

of ergotism having an etiological role in thrombo-angiitis obliterans.

In the ensuing four years, there appeared no further work to strengthen this hypothesis, so that we are forced to deny it the recognition of established fact.

In the interest of completeness, mention should be made of two other etiological theories.

In 1934, H.J. Gray (33) advanced the idea that thrombo-angiitis obliterans is the end-result of an intestinal putrefaction, with the resultant toxins in the blood stream having a selective action on the vascular intima.

In 1935, J.B. McDougall and J.H. Crawford (44) report a case of thrombo-angiitis obliterans in a gassed war veteran and advanced the theory that the toxic military gas was the etiology.

Both of these theories seem, for reasons quite obvious, quite untenable. Inasmuch as they have received no discernible support, they will be passed over with the euphemism of "Early and, as yet, unproven."

In 1936, Rabinowitz and Kahn <sup>(Path.60)</sup> (38) reported a derangement of phospholipin metabolism in thrombo-angiitis obliterans patients, and they felt this may play a part in the etiology of the disease. They found that, although phospholipins were mobilized into the blood stream, they were not properly stored or utilized in the form of creatine phosphate. Instead, there was a lowering of the lecithin to cephalin ratio (derivative products of phospholipin metabolism) and an absolute increase in the plasma cephalin. These workers felt

that, inasmuch as cephalin is an agent in the mechanism of clotting, increased cephalin in the blood must predispose to the intravascular clotting that is a feature in thrombo-angiitis obliterans. This work, it is seen, does not explain the inflammatory lesion, which, it will be seen, is believed to precede the thrombosis. However, this recent work may be found as touching on an accessory factor in the etiology; proof is dependent upon further investigation.

There is a feeling among certain workers in the field that the disease rests basically upon a disturbance in that "dark continent", the hypothalamus. It is felt that dysfunction here produces abnormal vasoconstriction that results in the disease. The idea is, at the present time, only a "hunch", and depends for its further evaluation and elucidation upon the discovery of the composition and function of this neurological "No man's land."

In concluding this section, it is seen that the etiology of thrombo-angiitis obliterans is, at the present time, unknown. The various theories have been presented with an attempt at evaluation thereof.

## P A T H O L O G Y

Thrombo-angiitis obliterans has been defined as "A clinical and pathological entity characterized by thrombotic occlusion of arteries alone or of arteries and veins....." Inasmuch as it is quite generally accepted that these divisions of the blood vascular system are the site of pathological involvement, it is reasonable to begin the discussion of the disease's pathology by a consideration of these parts. Buerger, of New York, was the first investigator to present a comprehensive study of the disease, particularly of its pathology. His findings have been accepted practically entirely without a dissenting voice; it therefore seems reasonable to present his work (6).

### GROSS PATHOLOGY

The deep vessels of the amputated legs regularly show an extensive obliteration of the larger arteries and veins. Besides this, there are two other lesions which vary greatly in their intensity, namely, the peri-arteritis and the arteriosclerosis. The appearance of the vessels on gross section depends upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessels, and that appears to be pierced at one

or a number of points by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency and does not at all resemble the crescentic or semi-lunar occluding masses typical of arteriosclerosis. The vessel itself is usually contracted, so that its wall appears to be somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old obliterating process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue. Frequently it becomes softer, more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the brownish tissue gives way to soft, reddish masses which are evidently the results of recent thrombosis. In some cases, this thrombotic process occupies larger portions of the vessel's course; in others, it is of short extent and terminates in a long cone of recent thrombosis.

The veins share equally with the arteries in the lesion of occlusion; in some cases, the veins are more extensively involved than the arteries.

Besides the lesion of occlusion, there are two other striking changes, namely, a certain amount of arteriosclerotic thickening and periarteritis. Arteriosclerosis is absent in the younger cases; when



present, it is never pronounced, except in those rare instances in which the patient has suffered from the disease for many years and has reached the age of forty or more. As a rule, we note but a very slight degree of whitening or thickening of the intima, here and there, in the patent portions of the vessels. In a very few cases, small atheromatous patches are present.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels. Wherever the vessels are occluded, there is apt to be an agglutinative process which binds together the artery and its collateral vein, and sometimes, also, the accompanying nerve, so that the liberation of the individual vessels by dissection is difficult. The adhesive condition is due to the fibrous tissue growth and varies considerably in its amount. The peri-arterial fibrosis varies, sometimes being almost absent, at other times so great that isolation of the vessels or nerves becomes impossible, and the vascular structures make up one dense rigid cord.

#### HISTOPATHOLOGY

The lesions may be considered in two stages:

- (1) The acute or incipient stage of thrombosis.
- (2) The healed or organized stage.

Between the earliest alterations in the deep arteries and veins and superficial veins and the finished product there are a large number

of intermediate pictures that illustrate the metamorphosis of the obturating clot into the intravascular cicatrix.

(1) The Acute or Specific Lesion.

The early lesions are so characteristic histologically that their appearances are practically specific for thrombo-angiitis obliterans and may permit the pathologist to make a diagnosis of the disease. They are rarely to be seen in the deep vessels for the reason that the patients do not allow amputation until the disease has lasted for months or years. However, they can be well studied when these are the seat of the typical migrating phlebitis, and have been shown by Buerger to be identical with the acute lesions in the deep vessels.

The earliest changes appear to be the usual evidences of an acute inflammatory process involving all the coats of the vessel. The media, adventitia, and perivascular tissues are infiltrated with polymorphonuclear leukocytes and the lumen of the vessel is completely filled with red clot. In the peripheral portions of the clot, larger or smaller foci of leukocytes (purulent foci) begin to form, whose growth occurs by virtue of the immigration of leukocytes. Then, certain peculiar giant-cell foci develop and are characteristic. They contain giant cells, endothelioid cells or angioblasts and numerous broken-down leukocytes. These foci then undergo connective tissue replacement. The giant cells gradually disappear; numerous small vessels are formed, the final product being a fibrous nodule containing vessels and some pigment. In the rest of the occluding clot the

organizing process is somewhat different, resembling that which characterizes the organization of blood clot in other thromboses.

(2) Healed or Organized Stage.

The most common lesion is a total obliteration of the lumina of arteries and veins by connective tissue. Histologically, this may be extremely varied in the general appearance, but each picture can be interpreted correctly as having its origin in the lesion of occlusive thrombosis. This obturating connective tissue usually harbors numerous small vessels, pigment containing hemosiderin, and a fair amount of connective-tissue cells. The canalizing vessels, when they become dilated, form smaller or larger sinuses, giving the fenestrated or cribriform lesion seen on microscopic section of the vessels, or when the canalizing vessel becomes eccentrically placed, and sufficiently large, this sinus is responsible for the appearances which have been incorrectly interpreted as the product of an endarteritis obliterans.

Elastic tissue stains demonstrate characteristic differences between this process and arteriosclerosis. Thus the region of the organized clot is almost completely free from elastic tissue. The small amount which is present is concentrically disposed about the new-formed vessels.

Still more suggestive and instructive is the finding of various stages of the disease in different members of the same vessel sheath. Thus a large artery affords a view of the old lesion as well

as one of its venal comites. Another accompanying vein, however, is in the "acute" stage of the disease, a smaller venule or satellite being in the intermediary stage, where certain military giant-cell foci make their appearance. Such pictures not only reveal the thrombotic nature of the disease but also present an argument in favor of the following two assumptions: That the disease begins with an inflammatory lesion attended with occlusive thrombosis, and that it affects the arteries and veins in a sort of relapsing fashion, very much in the same manner as in the veins in migrating phlebitis.

In short, the lesions in thrombo-angiitis obliterans are, in chronological order:

- (a) An acute inflammatory lesion with occlusive thrombosis, the formation of military giant-cell foci.
- (b) The stage of organization or healing, with the disappearance of the military giant-cell foci, the organization and canalization of the clot, the disappearance of the inflammatory products.
- (c) The development of fibrotic tissue in the adventitia that binds together the artery, vein and nerves.

As far as could be determined, the literature presents but one dissenting voice, that of Perla (22). This investigator stated that the lesions seen in migrating phlebitis described as characteristic for thrombo-angiitis obliterans by Buerger really are not specific. He went on to say that Buerger's so-called "specific

lesion" is never seen in the deeper arteries or veins, the primary seat of the disease. As stated, Perla's ~~was~~ the only dissenting voice, and in the twelve years that have passed since his contention (1925), he has found no corroboration. It therefore seems reasonable to accept Buerger's description.

#### CLINICAL PATHOLOGY

##### Distribution:

That thrombo-angiitis most frequently involves the blood vessels of the lower extremities has long been widely known and universally accepted Buerger (6) points out:

"The veins share equally with the arteries in the lesion of occlusions. In some cases, the veins are more extensively involved than the arteries, and this is particularly true of the collaterals of the posterior tibial which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or of the whole of the anterior tibial, occlusion of the dorsalis pedis and dorsal hallucis, of the posterior tibial and plantar vessels, with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely, a large portion of the dorsalis pedis is open, with the beginning of the occlusion in the upper half of this vessel or in the lower portion of the anterior tibial."

Jablons (19) reported the most frequent sites as: Dorsalis pedis, posterior tibial, peroneal, popliteal, and not infrequently the femoral.

Even at the present time many physicians are under the impression that thrombo-angiitis obliterans is a disease of the arteries and veins

of the extremities; the idea persists in certain text-books. This conception is not true; at best, it is only partly correct. Thrombo-angiitis obliterans is a disease of the blood vessels of the entire body; its apparent limitation to the arteries and veins of the extremities is due to the fact that the vessels of these parts are predisposed to insult by the mechanical factors involved in the circulation of dependent parts generally.

There are represented in the literature instances in which the disease has been found to involve vessels in almost every part of the body. In 1924, J. Meyer (18) described a case in which there were probably lesions in the intestinal vessels; the patient, a man suffering from thrombo-angiitis obliterans, presented symptoms of intermittent "claudication" involving the intestinal tract. Buerger, quoted in (19), reported spermatic vein involvement, and Spiegel (quoted in the same review) found involvement in the inferior mesenteric artery. Linenthal and Barron (51) presented two cases of cerebral vascular pathology in patients with thrombo-angiitis obliterans of the legs; they justified the contention that the intra-cranial pathology was thrombo-angiitis obliterans on the basis of the age of the patients (under fifty years) and the fact that there were no signs of arteriosclerosis. Samuels and Feinberg (42) presented fifty cases of thrombo-angiitis obliterans of which five showed definite clinical and electrocardiographic evidence of coronary involvement. Taube (44) presented two cases of thrombo-angiitis obliterans of the extremities that developed mesenteric thrombosis. Gresser (46) presented a case

of occlusion of the retinal vessels in a patient suffering from thrombo-angiitis obliterans; arteriosclerosis was ruled out. Birnbaum, Prinzmetal, and Connor (51) present<sup>ed</sup> a case of generalized thrombo-angiitis obliterans, verified by post-mortem examination; involvement was seen in cerebral, retinal, pulmonary, coronary, mesenteric, suprarenal, pancreatic, duodenal, hepatic, renal, and prostatic vessels - in addition to those of the extremities. Averbuck and Silbert (54), in a consideration of the causes of death in forty-seven patients that had thrombo-angiitis obliterans, found that such patients often died as a result of thromboses of arteries in the heart, brain, and intestines. "The frequency of such vascular involvement forces the conclusion that a bona fide association doubtless exists, and that the thrombotic occlusive manifestations outside the extremities are related to the established disease process." In June, 1936, Cohen and Barron (60) reviewed the literature on the autopsy material in thrombo-angiitis obliterans and concluded that thrombo-angiitis obliterans is a generalized disease process which may affect vessels anywhere in the body, giving a clinical syndrome dependent upon the vessels and organs affected.

It may be wise to point out here the possibility of aneurysms as part of the picture in thrombo-angiitis obliterans. In 1932, Pemberton and Mahorner (47) reported two cases in which aneurysms were associated with thrombo-angiitis obliterans. Four cases in all of aneurysms associated with thrombo-angiitis obliterans were described at the Mayo Clinic from 1919 to 1928. The authors stated, "The

pathogenicity of thrombo-angiitis obliterans makes it a not unlikely cause of aneurysm and the association of the two diseases is probably more than coincidental." Inasmuch as the literature is lacking in further word on this consideration, the question is not regarded as settled.

Blood Phenomena:

In view of the fact that intra-vascular clotting is one of the prime features of thrombo-angiitis obliterans, it is not at all surprising that many investigators in the field have based their researches on a study of the blood. We now turn to a consideration of their findings.

In regard to the blood viscosity (a point to be considered, inasmuch as it is a large factor in the phenomenon of clotting), there has been found an increase. (Koyano (10), in his study of the disease in one hundred and twenty Japanese, found a definite increase in viscosity. (This observation will be found significant - see "Therapy" - in that it furnished the basis for an established mode of treatment.) This observation was substantiated by Jablous (19) and Mayeshima (quoted in 19). Koyano reiterated his findings in a later study (17). Still further corroboration is seen in the work of Silbert, Kornzweig, and Friedlander (40) and of Silbert and Friedlander (43). The latter workers pointed out that the increase in viscosity does not seem to be a matter simply of dehydration.

The blood volume in thrombo-angiitis obliterans was found to be decreased. Silbert and Friedlander found an apparent relation to thyroid function (45).



In regard to figures for various blood constituents, there is not found to be complete agreement of opinion. Viewing the work on the nitrogenous constituents of the blood, Bernhard (9) found no increase over the normal figure. Later workers do not agree with this observation, for Jablons (19) reported a high uric acid figure. Silbert and Friedlander (43) reported an increase in total protein.

The blood cholesterol was found normal by Bernhard (9) and by Koyano. However, in the series of Heitz and of Troissier and Ravina, the figure was found to be definitely raised. The figure of Silbert and Friedlander (43) corroborated the latter.

Blood chlorides were found to be within normal limits by Bernhard (9) and by Silbert and Friedlander (43).

The blood calcium figure was found normal by Bernhard (9), but in the studies of Kahn (quoted in 19) and of Silbert and Friedlander (43), it was found increased.

Willy Meyer (8) found an apparent abnormality in the glucose tolerance, reporting a curve similar in shape to those of the normal and the diabetic, but intermediate in height. This was not substantiated by later workers. In Bernhard's series, 92% of cases had a normal curve, while 8% showed 200 mg. per cent or more at the end of two hours. This was not borne out in the work of later observers; Meleney and Miller (quoted in 19) and Silbert and Friedlander (43) reported normal figures.

The blood concentration is apparently increased; this was

shown by Koyano (10), Jablons (19), and by Silbert and Friedlander (43).

Thomas (13) reported a case of thrombo-angiitis obliterans in which he had found a persistent leucocytosis. The literature furnishes no corroborative work since this report.

In 1933, Rabinowitz (49) reported an apparent derangement of phospholipin metabolism; he found an increased lecithin content in the blood in thrombo-angiitis obliterans cases. He felt this is linked with the fact that choline (which is easily split off from lecithin) is found in abundant quantities in the urine (his series). He further believes this is connected with the fact that he has found the myelin of the nerves (which is rich in lecithin) to undergo almost complete absorption in thrombo-angiitis obliterans cases. He believes (60), "Phospholipins are mobilized into the blood stream, but not properly stored or utilized in the formation of creatine phosphate which is necessary in normal muscle activity." At the present time, this line of investigation rests uncorroborated.

Summarizing, it seems accepted that, in regard to blood figures in thrombo-angiitis obliterans, there is:

- (1) Increased viscosity.
- (2) Increased concentration.
- (3) Decreased volume.
- (4) Increased calcium.
- (5) Normal chlorides.
- (6) Normal glucose tolerance.
- (7) Other figures remain unconfirmed or equivocal.

In conclusion of this section devoted to a consideration of the pathology of thrombo-angiitis obliterans, there has been considered the gross and microscopic pathology of the disease, the distribution of lesions, and the blood phenomena.

### SYMPTOMATOLOGY AND DIAGNOSIS

Buerger ("Pathology" 6) defined thrombo-angiitis obliterans as "a clinical and pathological entity....giving subjective manifestations, chief among which are: Pain and the peculiar symptoms of intermittent claudication; and presenting objective phenomena, the most important of which are - redness in the dependent position of the limb, marked blanching in the elevated position, evidence of arterial occlusion in the form of pulseless vessels, trophic disturbances of moderate extent, and of even grave consequence, often terminating in gangrene of one or both lower extremities." As stated, this definition includes the main symptoms and findings; elaboration of, and addition to these points will be attempted in the ensuing section.

#### SYMPTOMS

##### Pain:

Probably the most frequent cause of bringing patients, in general, to seek medical aid is the symptom of pain. This is found true in the instance of thrombo-angiitis obliterans. Before discussing the subject of pain in this disease, it is well to point out the variability of this general subjective manifestation. It is well known that reactions to pain vary widely from individual to individual; Libman's test, (degree of pain perceived when <sup>digital</sup> pressure is exerted over the tips of the mastoid processes) performed upon

large series of patients, serves to illustrate this truth. Therefore, in evaluating the story of any patient, due consideration should be given to the patient's reaction-type.

There are, generally, two types of pain in thrombo-angiitis obliterans:

(a) Intermittent Claudication:

This type of pain is observed to have two important characteristics - (1) pain and/or cramp that is brought on by exercise of the involved part, (2) relief by rest. The pain is most frequently experienced in the calf of the leg; other common sites are the foot, ankle, and patellar area. As noted, however, this symptom occurs in relation to the involved part; in "Pathology" a case is referred to where it was noted in relation to the gastrointestinal tract. The production of the pain is quite well agreed upon. Brown and Henderson (11) voiced the common belief that "it is an expression of anoxemia and indicates deficient supply of blood for the muscles under conditions of work". Lewis postulated the formation of an "X" substance within the muscle. Rabinowitz feels the basis may be found in an abnormal phospholipin metabolism (See "Etiology"). Generally, it is believed, as indicated, that some products of muscle metabolism accumulate, due to lack of their oxidation by oxygen normally supplied by unimpaired circulation; this seems reasonable on the basis of aggravation by exercise and relief by rest.

It must be appreciated that intermittent claudication is

one of the most frequent symptoms and may be noted as the only symptom for a varying period before the appearance of other symptoms or signs. In Perla's series of forty-one cases (9), it was the only symptom for from several months to as long as five years before the appearance of other symptoms. In the series of Brown and Henderson (11), it was the first symptom in fifty-one per cent of cases, and existed for periods the shortest of which was two months and the longest fifteen years. The same authors noted a variation of this symptom in the form of abnormal fatigue that comes on, especially in one rather than in both legs, upon the performance of an "ordinary" amount of exercise.

Simmons (38), in 1936, devised a mechanical aid for the measurement of intermittent claudication, which he called the "ergometer". Essentially, this is a machine which enables an observer to count the number of times the patient can lift a known weight through a uniform distance by dorsiflexion of the foot. Intermittent claudication is denoted by the number of times the foot is flexed in order to produce noticeable pain and to tire the muscles to the point of exhaustion so that no lifting is possible without a rest period. This device may become widely accepted as a diagnostic and prognostic aid; at present, it is usual to inquire of the patient how many blocks he can walk.

(b) "Rest" Pain:

This type of pain typically occurs late in the disease,

practically always after numerous other subjective and objective signs are present. It is a steady, constant, burning, tormenting pain that is apparently worse at night. The basis for the pain, as yet undetermined, finds possible elucidation in two theories. The first postulates that it is due to imminent tissue death in a part, the circulation of which is seriously compromised. The second points to the peri-arteritis elucidated by Buerger as part of the disease-process and bases the pain upon involvement of the contiguous nerves by the fibrous tissue which tends to contract down upon the nerve with the passing of time. In many cases, this may seem valid, since the nerve may be seen to be closely matted with the connective tissue, <sup>however,</sup> while, other cases, in which there is severe pain, may show clean nerves.

This pain, which is unassociated with exercise, cannot be over-emphasized in point of its severity. Many cases do not yield to morphia and cause the patients to plead for amputation. Buerger noted that this symptom may, directly or indirectly, lead to apparent mental derangement.

Another type of pain - associated with the so-called migratory thrombophlebitis - is observed in thrombo-angiitis obliterans. It will be noted under the remarks on the vein involvement.

#### Sensation of Coldness in the Involved Part:

Patients frequently complain of a feeling of coldness in the hands or feet, depending upon the site of involvement. This is

often preceded by a feeling of numbness or stiffness in the fingers or toes. Although the degree of coldness varies, the sensation may become so intense that the patient feels he is walking on ice. This symptom is based apparently upon the impairment of circulation; Jablons ( 8) noted that if the circulation improves the coldness gives way to a comfortable sensation of warmth and the toes and fingers no longer feel stiff. This symptom does not seem to have the diagnostic importance of intermittent claudication. In the series of Brown and Henderson (11), coldness of the extremities was the first symptom in twelve per cent of cases, while it had been pointed out that intermittent claudication -- often called the symptom par excellence of thrombo-angiitis obliterans - was the first symptom in fifty-one per cent.

#### Migratory Thrombophlebitis:

This condition, denoting involvement of a superficial vein, is seen in about twenty per cent of cases. The most common site is the internal saphenous; other sites are the external saphenous, radial, and ulnar. There may be simultaneous or intermittent involvement of more than one vein. The involvement usually shows itself in the form of small, red, nodular areas denoting the condition in various lengths of the vein. The areas affected are from one to four inches long, often multiple, and frequently involve adjacent structures. The pain is variable; in some cases there may be none at all, while in others there is intense subjective reaction.

The pain varies from dull to sharp and burning; in some cases manifested as a sense of "tightness."

Upon palpation, the swelling is doughy in the acute stage and later becomes firm. When the swelling subsides, the vein may be noted as a fibrous cord or as a brownish streak.

#### PHYSICAL EXAMINATION

Although certain sources hold that physical diagnosis is rapidly becoming a lost art, soon to be replaced by more accurate methods, such as X-Ray, electrocardiography, etc., the use of the ordinary physical senses still stands the physician in good stead. The thus discernible features in thrombo-angiitis obliterans will now be discussed. Two modes of examination have importance, namely, inspection and palpation; where they are to be supplemented by mechanical aids, appropriate discussion is included.

In observing the general appearance of the limb, it is important to observe any departure from the normal. Skin changes are seen in the form of fissures, ulcers, bullae, ecchymoses, impaired nail growth, gangrenous areas, signs of infection, lymphangitis, and venous thrombosis (described above), evidence of malnutrition, such as atrophy, exceptional prominence of bony landmarks and tendons. Variations from the normal color, particularly marked pallor in the elevated position, increased redness on dependency, cyanosis -- all of which are manifestations of impaired circulation.

The nails, in the early stages of impaired circulation,



show a slight vertical ridging which may be associated with a greyish-black discoloration that, in some cases, extends down to the half-moon of the nails. The growth of the nails may be definitely slowed; when the condition of the circulation improves, the rate of nail growth becomes more rapid and in some cases there is observed an appreciable degree of hyperkeratinization.

Color Changes:

Inasmuch as the skin color depends upon the state of the circulation (and certain other factors, such as thickness of the skin, pigmentation, etc.) important information may be derived in this condition, a prime feature of which is impairment of the circulatory state.

While color changes may be apparent when the limb is in the horizontal position, they are much intensified by elevation and/or dependence. With the limb in the pendant position, and in the absence of inflammation, a red flush involves the toes (fingers) and dorsum, as well as the sole (palm) of the foot (or hand) extending upward for a variable distance, rarely further than the ankle (or wrist). This is a phenomenon seen in many cases of occlusive vascular disease; it is known as rubor or erythromelia (not to be confused with erythromelalgia). It is believed to be brought about by a compensatory dilatation of the superficial capillaries, and is most characteristic of thrombo-angiitis obliterans, although found in other arterial affections attended by closure of larger vessels (Buerger 5). Although more striking in the pendant position, the

rubor may also be present in the horizontal position, and when continuously in evidence, is termed "chronic rubor" or "chronic erythromelia", in contra-distinction to "reactionary rubor" that may be induced by depressing the limb after previous elevation.

When the affected limb is elevated, blanching becomes apparent, with rapidity in direct ratio to the amount of involvement. The extent of blanching and the rapidity with which it occurs may be of aid in estimating the degree of arterial occlusion. When the affected limb is cold, the tips of the toes may remain slightly blue or cyanotic. Should the blanching be slow in appearing, or very hard to determine, pressure upon the tips of the toes after the limb has been elevated for some time will show whether or not the part has become depleted of blood. Compression of the toes of the elevated foot in normal cases will reveal the presence of sufficient bright arterial blood (rarely, slightly cyanotic) while a varying degree of ischemia, with or without marked cyanosis, will accompany obliterated or obstructed arteries.

Buerger's observations led him to formulate the "angle of circulatory sufficiency." The estimation of the angle is based on the supposition that the normal limb, when elevated so as to be perpendicular to the horizontal plane ("angle of 180 degrees") still retains most of its color. When the circulatory mechanism is defective and the limb is elevated to the vertical, a variable degree of blanching of the foot occurs. If the leg is then gradually depressed, the angle at which a reddish hue returns - the angle of circulatory sufficiency - will be found to vary considerably. In

some cases, it will be necessary to depress the limb to the horizontal before evidence of returned circulation is manifest. The angle of circulatory sufficiency would then be ninety degrees.

In many cases of arterial disease the estimation of this angle is a valuable adjuvant, not only in the recognition of the extent of the circulatory disturbance, but also in prognosis (5).

Buerger (5) also formulated the sign of "reactionary rubor" (or reactionary erythromelia). This refers to an induced rubor that manifests itself in the pendant position of the foot after the limb has been previously elevated to the vertical. It is a physiological phenomenon that blanching of a limb artificially produced by an Esmarch or Martin bandage will be followed by dilatation of the capillaries of the peripheral parts when the circulation is allowed to return. So, also, blanching will occur in a limb whose larger arteries are occluded on mere elevation sixty to ninety degrees above the horizontal. When such a limb is then depressed to the pendant position, a similar induced or reactionary rubor will become manifest. This well-known manifestation may be invoked in the examination of cases in which impaired circulation due to arterial occlusion is suspected. "It is found particularly useful in thrombo-angiitis obliterans, although also demonstrable in other cases of organic vascular disease. In early cases, it is especially valuable, for it may be present long before the chronic condition of rubor or erythromelia develops." (5)

During the history of our knowledge of the disease, certain tests have been devised, based upon color changes in affected parts. Samuels (15), in 1929, reporting on "plantar ischemia", gave a resume of these tests. Oehler, in 1907, had noticed blanching of the hand produced by rapid opening and closing of the fingers in an obscure neuro-circulatory affection of the upper extremities. Parkes-Weber, in 1908, applied this manoeuvre to the feet in cases of thrombo-angiitis obliterans and observed that when the feet were kept in the dependent position until the characteristic redness appeared, and then a rapid flexion and extension carried out, the redness would be replaced by a temporary pallor. Samuels, in 1929, modified this procedure and described the technic in the test he called "plantar ischemia":

"The patient lies on his back with feet in the vertical position. He is then instructed to carry out a rapid flexion and extension of both feet at the ankle joints. The observer keeps careful watch of the soles of both feet. If there is arterial occlusion, there soon becomes manifest a definite pallor of the sole of the affected extremity. If the occlusion is extensive, the pallor is complete, producing a cadaveric appearance in the affected sole. If the opposite limb happens to be normal, the marked contrast between its pinkish sole and the pale sole of the diseased leg is easily evident. If the arterial obstruction is not very extensive, as in an early case, the pallor will have an uneven distribution

and will usually be seen in the big toe alone or at the bases of all the toes, or it may show as a diffuse mottling of the sole, readily distinguishable from the diffuse pink of the normal foot. This pallor is produced, I believe, by the double action of gravity plus the squeezing action of the muscles of the legs, which depletes the foot of the little blood it contains. I must repeat that this test is exquisitely sensitive and should be used in every suspected case of arterial disease."

The same year, Allen discussed the diagnosis of chronic occlusive arterial lesions distal to the wrist. He reported (16) on two tests he had found valuable. The first concerns itself with occlusion of radial or ulnar arteries. The technic is, essentially: The patient clenches both hands tightly for one minute to drive the blood out of the hand - the examiner compresses (digitally) the radial arteries of both wrists. The patient opens the hands and the color of the palmar surfaces is observed. Ulnar occlusion will be indicated in delayed return of color in the affected hand. Repeat for the radial artery by compressing the ulnar arteries.

Allen tested for the digital circulation with his so-called "stroke" test. The suspected digit is stroked heavily (ironing out the normal color). In individuals with obstruction of the digital arteries, the pallor is maintained for a prolonged period. The test is best carried out with the hands elevated. The same result is observed after compressing the digit for five seconds between the examiner's thumb and index finger.

Visible skin changes, symptomatic of a more advanced degree of circulatory impairment, occur in the form of fissures, ulcers, and gangrene. Fissures (essentially linear ulcers) develop after a variable period (months or years). The common sites, according to Jablons (8), are the plantar surfaces of the toes in the skin folds corresponding to the inter-phalangeal articulations, in the "web" between the toes, and at the base of the toes. Fissures are very painful and are seen to be of varying depth - in some cases going down as much as half an inch. Two factors seem involved in the production of fissures: (a) Devitalization of tissues due to impaired circulation and (b) the exciting action of maceration (fluid used in local therapy and sweating) and friction or other forms of trauma. Fissures often give rise to the common variety of ulcer. The common sites for ulcers are the inner and outer margins of the big toe adjacent to the nail, the outer aspect of the little toe, the middle of the second toe. The ulcers are characteristically irregular in shape, punched-out with overhanging edges, and giving little or no secretion. They usually extend down to the superficial fascia but may, in certain cases, go down as far as the bone.

Gangrene is the practical end of the pathological road in occlusive arterial disease. It may occur spontaneously or be preceded by fissure and/or ulcer. The big toe is the most frequent site, although it may be seen in any toe or on any portion of the

foot. It is rare, however, for the area of gangrene to extend proximal to the annular ligament. Jablons (8) reported that superficial gangrene of the skin and subcutaneous tissue often occurs, affecting, usually, the tissue over the anterior part of the leg. Samuels (Therapy 51) gave a summary of the clinical concept of gangrene. He stressed the fact that not every case of thrombo-angiitis obliterans terminates in gangrene. It must be realized that, hand in hand with the pathological process, there proceeds the development of a collateral circulation, so that extensive occlusion may exist without the necessary occurrence of gangrene. As long as the balance between obliteration and the development of collateral circulation is maintained, gangrene will not set in. However, should the balance be swayed against the development of collateral circulation (occlusion of sudden nature, continuance of smoking, frost-bite, etc.), gangrene will set in. It is important to realize that the pathological process of occlusive arterial disease tends to be one of self-limitation. When the arterial circulation becomes insufficient to maintain the viability of the part, tissue death sets in, and is signalled by the pain of impending gangrene. With the development of gangrene, the pain leaves the site and is localized at the line of demarcation. However, should infection occur, the tissue becomes swollen, liquefaction necrosis sets in, possibly giving an ascending lymphangitis which is followed by extension of the gangrene.

Palpation:

In this form of physical diagnosis, two general findings are available that point to occlusive arterial disease. These are coldness and absence of normal pulses.

Coldness, or abnormal lack of heat, would be expected in conditions a prime feature of which is circulatory impairment. Again, as it would be logical to believe, the degree of coldness varies in direct ratio to the extent of involvement of the circulation. Coldness is most apt to be noted in the most peripheral portions, such that the tips of the toes and fingers are especially to be observed. Many cases will demonstrate coldness that is apparent to the palpating hand, but there are cases in which the involvement is not sufficiently great to produce change that is noted by the relatively crude temperature sense of the hand. To assist the human senses, mechanical devices have been produced. Probably the most sensitive of these is the so-called "Dermotherm" (Tyco),<sup>a</sup> a thermocouple arrangement which electrically compares the skin temperature against a given constant temperature (furnished by water in a Dewar flask - "thermos" bottle). This device is valuable in the determination of skin temperatures, especially in certain technics devoted to the problem of ascertaining the element of vaso-spasm (discussed below). However, inasmuch as this instrument represents an expenditure in the neighborhood of two hundred dollars and is quite specialized in its application, it is seldom found out-



side of well-equipped clinics. The practitioner finds available a mercury thermometer that may be adapted to skin temperature determination (attachments to insure constant, even contact with the skin). This type of thermometer is much less costly, and, for practical purposes, is quite satisfactory.

The figures for skin temperatures vary somewhat among the various workers, but the normal range is generally accepted as twenty-nine to thirty-five degrees Centigrade. It should be mentioned that the skin temperature varies according to the site on the body surface measured. Temperatures of less than twenty-nine degrees Centigrade are conceded to be indicative of abnormal lack of heat. It is understood that certain conditions are to be observed in the determination of skin temperatures. Essentially, they involve a room the temperature of which is relatively constant at about seventy degrees Fahrenheit (no drafts!); the part observed is exposed to the room temperature for about twenty minutes before readings are taken. More detailed conditions are outlined below under "Therapy", in relation to work involving the selection of cases for sympathectomy.

The second finding discernible by palpation concerns the perception of peripheral pulses. Normally, the palpable pulses discerned are the dorsalis pedis, posterior tibial, radial, ulnar (to some extent), the femoral, and, in patients not presenting obesity or edema, the popliteal. A word seems appropriate regarding the technic of palpating arterial pulsations. The dorsalis pedis is

usually palpated between the heads of the first and second metatarsals. This pulse is quite superficial and may easily be obliterated by undue pressure in palpation. It not infrequently pursues an aberrant course, and so it is wise to palpate across the dorsum of the foot. The posterior tibial is palpated about one inch behind and above the internal malleolus. If present it is usually easily perceptible. The radial and ulnar pulses are obtained in the usual manner. The femoral pulse is felt in the femoral triangle, just beneath the inguinal ligament, about mid-way between the pubic crest and the anterior superior iliac spine; pulsations are quite easily palpable when present. Palpation of the popliteal artery may offer some difficulty. It is important to have the patient in the correct position. The patient lies prone and the hamstring tendons are relaxed. This last point is quite important and failure to appreciate it may well result in the missing of a pulse that is present. The hamstring tendons are relaxed by holding the leg and telling the patient to leave it alone, "let it fall". Relaxation of the tendons is verified by palpation at the borders of the popliteal fossa. The palpating finger tips are then pressed steadily into the center of the fossa. Pulsations, when present, are perceptible after a few seconds' interval. One must be sure, in palpating pulses, to support his hand below the wrist, if possible, else sensitivity is bound to suffer when the weight of the whole arm above rests upon the fingers. Thus, when

palpating the dorsalis pedis, posterior tibial, radial, and ulnar, the observer rests his hand upon the ankle or wrist by letting the interval between the thumb and index finger support his hand upon the patient's respective joint, while employing the tips of the three middle fingers in palpation. One must be careful lest he perceive his own pulse and attribute it to the patient. This may be avoided by timing his own and known pulses in the patient or by touching the fingers of the free hand to a hard surface and comparing his pulse so obtained with the one he thinks is felt in the patient. These remarks on the palpation of pulses may seem unduly elementary, but they are presented because of their apparent importance.

In the original description of the disease, Buerger pointed out the prime importance of absent pulses in the diagnosis of occlusive arterial disease; this point has been pointed out, corroborated, and stressed universally by subsequent workers. The mechanism of the suppression of pulses seems fairly clear when one considers the pathology of occlusive arterial diseases. In all, the obliteration of the vascular lumen stops the passage of the pulsating blood flow, additionally, perivascular reaction, especially in thrombo-angiitis obliterans, may bind the vessel tightly. However, the palpation of pulses does not furnish absolutely impeccable information. Pulses may actually exist but be not perceptible -- this is seen particularly in the cases of the dorsalis pedis (a certain percentage are "normally" unpalpable - Reich 30) and the popliteal. Again, cases may

be encountered in which involved arteries give pulsations. This condition, not common, was pointed out by Buerger (5) and by Allen and Brown (12).

Oscillometer:

Here again, a mechanical aid is available to extend the limits presented by human senses. The oscillometer, a device for the detection and measurement of arterial pulsation, was devised by Pachon in the beginning of the second decade of this century. In 1914, Matas (3), reviewing diagnostic methods of that time, mentioned it as being too young to be evaluated. It was used to some degree for years by French workers, but it was not until 1927 that it was to any extent taken up in the United States. In 1927, Samuels (10) called attention to it and advised general application of its use.

The oscillometer consists essentially of a closed air-pressure system that registers changed pressure produced within the system by arterial pulsation communicated to a pneumatic cuff placed around the part. A bulb hand-pump inflates the cuff to any desired pressure which is read from a dial connected with the system. Also connected with the system is a rigid, hermetically-sealed metallic box containing an aneroid capsule. An escape valve permits the release of pressure, and a cut-off arrangement allows isolation of the cuff-anaeroid system from the hand pump-pressure-dial system. When this is performed, the rhythmic variations in the volume of the segment of the limb under any desired pressure are transmitted

only to the anaeroid capsule (not to the cut-off) which, in turn, transmits its variations to a visible needle.

The oscillometric index, as given by the amplitude of the excursions of the needle, is a measure of the cardiac impulse and conforms to the total pulse of the segment of the limb under investigation. Figures for the oscillometric index, obtained from a large series of normals, furnished standards; deviation from these implies circulatory impairment.

Upper Extremity:

Upper Arm: 4 -20  
 Elbow: 2 -12  
 Wrist: 1 -10  
 Palm: Very faint -2

Lower Extremity:

Thigh: 4- 16  
 Upper third of leg: 3 -12  
 Ankle: 1-10  
 Tarsal: Less than 0.5 - 2

Samuels pointed out that the use of the oscillometer has definite advantages over palpation:

- (1) It permits the perception of very small pulsations that would escape palpation.
- (2) Furnishes measurement of the pulse at areas where arterial pulsation is not accessible to palpation (middle of leg, etc.).
- (3) Minute changes in amplitude of oscillation can be numerically studied and recorded for comparative quantitative measurement.

While these advantages are quite definite, the instrument is not an ideal aid. It cannot measure the non-pulsatile, seeping blood flow that may permit advanced cases of thrombo-angiitis obliterans to continue without signs of gangrene. Again, it cannot select any one vessel for study - an advantage retained by palpation.

Clinical value in the fields of differential diagnosis and prognosis is claimed for the oscillometer. Further discussion will be found below in a consideration of these phases.

Recently, a preliminary report was given which may provide another mechanical aid for the determination of pulsations in a suspected lower extremity. In 1935, Bernheim (32) presented his beginning work on a graphic method of interpreting vascular disease of the legs. Essentially, this method depends upon the fact that when the normal individual sits with legs crossed, there is an almost invisible swing of the foot that is synchronous with the heart beat. The author attempted no explanation for the phenomenon but tried to employ it by recording it upon a smoked drum (Kymograph). A simple technic was used; a recording rod, tipped with a pointed bit of photographic film, was attached to the shoe and placed in contact with a drum revolving at constant speed. Bernheim found normal tracings to show a dicrotic wave, and corresponded closely to radial artery tracings. In patients with vascular disease of the legs, the swing was much less than normal or entirely absent, depending upon the extent of popliteal artery involvement and the status of the collateral circulation. A tremor, found in normals, was much more prominent in the diseased. This method may furnish a valuable index to circulatory state, progress, and prognosis; but inasmuch as no further study is available beyond the preliminary report, evaluation must be suspended.

Arteriography:

Roentgenology, in spite of its comparative youth, has already been investigated from a view of being an aid in the study of peripheral vascular disease. Edwards (27) gave a comprehensive history of vasography, which study has centered mainly about the quest for satisfactory media.

Trendelenburg, in 1902, was the first to describe an opaque substance within the circulation. His patient had been shot in the heart; on X-Ray the shot could be seen, moving to and fro with the moving blood. In 1903, Riethus described the X-Ray appearance of foreign bodies introduced into the hearts of dogs via the jugular vein. The first experiments with a liquid medium were performed by Franck and Alwens, in dogs and rabbits; bismuth in oil was the medium used and which was soon discarded because of the danger of embolism.

The earliest good vasograms in humans were secured by Berberich and Hirsch who used ten to twenty per cent of strontium bromide. In 1924, Brooks obtained good results with sodium iodide (50% solution); this medium, however, was found to be too irritating. Lipiodol was next tried, but, as may be expected, was soon abandoned because of the danger of embolism; it had, also, the disadvantage of being too viscid to be introduced quickly through a fine gauge needle. These disadvantages were overcome, to some extent, by emulsifying the lipiodol. In 1930, Saito et al (17) reported on

the use of this emulsion ("Protalbin-albuminic acid", lecithin and glucose). They used as much as 20 c.c. without ill effect. Edwards (27) reported, "This type of medium remains as one deserving further use and observation."

Thorotrast (25% aqueous solution of thorium dioxide with a colloidal carbohydrate) was introduced by Radt in 1930. Edwards concluded that, although it is the most opaque of media, it "comprises a menace of unknown proportion" due to the radio-activity of the thorium held in a more or less permanent combination throughout the reticulo-endothelial system. Blumgart, of Boston, in a personal communication to Edwards summed it up, "Don't use it (Thorotrast) if your patient is not going to be dead of some other cause in less than a year." More will be heard in relation to this medium from the studies of Allen and Camp.

Edwards (27) gave full approval of "Skiodan" (called 'Abrodil' in Europe), which is a mono-iodo-methane of iodine in firm combination. A 40% solution is sterile and stable, casts a good shadow, is freely miscible with blood, easily injected, and caused only mild discomfort. It is almost entirely excreted by the kidneys in two hours and its lack of general toxicity was proved by Heathcote and Gardner in 1931." This was corroborated by the work of J. Schuller and of Frey and Zwerg. Pearse and Warren, in 1931, subjected Skiodan to a rigorous test. They filled emptied portions of arteries in dogs with a fifty per cent solution and allowed it



to act undiluted for one to five minutes before removing the occluding clamps. On examination one to two days later, the vessels were free of any discernible damage. Edwards himself used Skiodan and found it very satisfactory in view of good visualization and freedom from deleterious action, even when injected outside the artery.

Allen and Camp did not share Edwards' condemnation of Thorotrast. In 1934 (29) they reported on its use and noted that they had observed no bad results at the end of three and one-half years. In 1935 (31) they reiterated the value of this medium. They found it the ideal arteriographic substance and, "The immediate toxic effect of small amounts appear to be mild, of little importance, and of rare occurrence ..... the possibility of eventual harm due to radio-activity can best be summarized as 'suspected but not proved'." They quoted Erickson and Rigler as having observed no ill-effects in the use of thorotrast in visualization of the liver and spleen.

The technic, as given by Allen and Camp, follows:

"The patient lies on the roentgenographic table with the film under his outstretched supinated arm. An ordinary sphygmomanometer cuff is wrapped about the arm as near the shoulder as possible. Under aseptic conditions, the skin and tissues around the brachial artery, just above the lacertus fibrosus, are anesthetized with 1 or 2 c.c. of 0.5% procaine. Radiopaque solution is injected into the brachial artery while the cuff compresses the arm well above the systolic pressure. The first roentgenogram is made. The cuff is quickly deflated to the level of the diastolic

pressure for two to four beats, to permit the material to be carried distally. The cuff is reinflated to its previous pressure and the second roentgenogram is made. The procedure is repeated for a third film. Additional films may be made with the arm in pronation or in the lateral position. The cuff is removed and with a gauze sponge firm pressure is made over the point of puncture for a few minutes. Essentially the same procedure is employed in the case of the lower extremity, except that digital pressure replaces the cuff and the femoral artery is entered near the base of the femoral triangle."

Points to be observed in the interpretation of arteriograms are (Allen and Camp):

- (1) Congenital variations from the usual formation of the vascular system.
- (2) Alterations in the lumina of the arteries, consisting of irregularities in contour, diminution of caliber, and complete occlusion.
- (3) Presence or absence of a collateral circulation; its situation and extent.

#### The Normal Arteriogram

- (1) Smooth and uninterrupted contour of the lumina of the injected arteries.
- (2) Direct course of these vessels.
- (3) Presence of no more than a minimum of collateral circulation.
- (4) Spasm is characterized by smooth diminution in caliber to a point of complete or almost complete obliteration, and an increase in size up to normal. This appearance may vary or disappear in subsequent films.

Thrombo-angiitis obliterans Arteriogram

(1) Primary Phase:

Change in the contour of a segment of an artery - instead of being smooth, the contour is irregular and the lumen varies in size; filling defects are usually rounded in contour.

(2) Secondary Phase

The shadow is shaggy and moth-eaten in appearance; the lumen is greatly reduced in size and pursues an irregular, ever-changing course; the channel may be divided in places as an island divides a stream.

(3) Final Phase

Complete occlusion; the point of occlusion is not abrupt, as if the artery had been ligated or sectioned, but rounded, with the convexity toward the occluded portion.

Collateral Arteries: The size, number, and course of these vessels is remarkable.

Further reference will be made to arteriography in the consideration of differential diagnosis.

DIAGNOSIS

The typical clear-cut case of thrombo-angiitis obliterans presents a characteristic and more or less unmistakable picture: The patient, a heavy smoker, usually a man in his twenties, thirties or early forties, complains of pain in the calf of one leg or in one leg more than the other. This pain is of the nature of a cramp, provoked by walking and relieved by resting for a few minutes. The

pain comes on after a fairly constant distance and may be associated with a sensation of coldness. The patient tells of noticing that his leg is red when it hangs down and becomes pale when held up in the air. There may or may not be a story indicative of superficial phlebitis. Physical examination will show the characteristic color changes and an angle of circulatory sufficiency indicative of occlusive arterial disease. Palpation will show absence of any or all of those <sup>pulses</sup> relative to the dorsalis pedis (especially), posterior tibial, and popliteal arteries, and the involved foot will feel colder than its opposite fellow. Skin temperature readings will bear out palpation and deviations from the normal will be present in the results of oscillometry and arteriography. At later stages, there will be seen trophic changes indicative of circulatory impairment: decreased nail growth, fissures, ulcers, and finally gangrene. The later stages are characterized by the constant, burning, tormenting "rest pain" that has no relation to exercise and is so severe as to often be unrelieved by morphia.

Unfortunately, all cases aren't such clear-cut unmistakable syndromes. Any combination of signs and symptoms may occur, and the sequence of their appearance may vary with apparently inexplicable lack of order. This is believed to be due to the fact that, while the occlusive process goes on, there proceeds concomitantly the development of a collateral circulation. Various factors may affect the maintenance of circulatory balance; this had been pointed out in the discussion of gangrene (above). Buerger pointed out that cases

tend to fall into twelve clinical types. These are named in a manner quite characteristic of the syndrome presented by history and findings:

- Type I. The slowly progressive.
- Type II. The non-progressive.
- Type III. The early compensated.
- Type IV. The acute fulminating.
- Type V. Gangrene without pain.
- Type VI. With venous involvement only.
- Type VII. With pulsating pedal arteries.
- Type IX. With associated arteriosclerosis.
- Type X. Without symptoms.
- Type XI. With sudden vascular occlusion.
- Type XII. With severe rest pain without trophic changes.

Differential Diagnosis:

The diagnosis of thrombo-angiitis obliterans requires differentiation from other circulatory disturbances of the limbs. These tend to fall into two main groups, depending upon whether the pathology is of an organic or a functional basis. Brown and Henderson (11) offer a comprehensive classification in the Table:

Functional Or Vasomotor Types	Local Distribution	Vaso- constricting types	( 1. Multiple-phase color reaction; Raynaud's disease.
			( 2. One phase color reaction; acrocyanosis, dead finger, local syncope.
	General Distribution	Vaso- dilating types	( Erythromelalgia
			( Vaso- constricting types
		Vaso- dilating types	( Primary or essential hypertension.
			( Arteriosclerosis
Organic Types	Local Distribution		( 1. Arteriosclerosis, with or without thrombosis; diabetic gangrene.
			( 2. Thrombo-angiitis obliterans.
	General Distribution		( 3. Simple thrombosis or embolism.
			( 4. Arteritis of known infectious origin (rheumatic, luetic).
			( 5. Aneurysm with or without thrombosis.
			( 1. Primary.
			( 2. Secondary to hypertension.

Raynaud's disease is a vasomotor disturbance that occurs typically in women (ninety-five per cent), in the age range, generally, of seventeen to thirty-five, and characterized by attacks of bilateral local cyanosis that do not often result in gangrene. Severe osseous change (absorption of phalanges) is frequently seen. Inasmuch as this is a purely vasomotor disturbance, pulsations are always present in the arteries of the involved limbs; the upper extremities are most subject to the disturbance. The functional vasomotor element can be demonstrated by subjecting the limbs to the effects of reflex vasodilation. The simplest method is that of Landis and Gibbon(26-A) in which the opposite limbs are immersed in warm water (about forty-five degrees Centigrade for twenty minutes). After this, the skin temperature of the affected limb, previously determined, is found to be increased. Other tests involve the use of the oscillometer. Babinski and Heitz (quoted in 10) claimed to differentiate between occlusive and functional arterial disease by immersing the limb in a warm bath for ten minutes and finding a marked increase in cases of vasomotor spasm but not in occlusive disease. This technic nor the following one have received appreciable mention in the literature. The second oscillometric method concerns the work of D'Elsmitz and Cornil (quoted in 10), who employed a tourniquet about the limb for about five minutes. On release of the tourniquet a marked increase in the oscillometric index was observed in vasomotor cases but not in occlusive.

A method quite generally accepted to demonstrate vasomotor spasm involves novocaine injection of the posterior tibial nerve as it passes behind the internal malleolus. The skin temperature is measured before, and at given intervals after the injection. Increased temperature after the thus-obtained release from sympathetic control indicates the presence of vasomotor spasm.

Radiologic study show absorption of the terminal phalanges to be a rather frequent occurrence in Raynaud's disease; this is rare in thrombo-angiitis obliterans.

Erythromelalgia is a rare clinical syndrome having its basis in a functional vasodilatation and characterized by paroxysmal attacks of pain and redness in the distal parts of the feet and more rarely the hands. It is differentiated by thrombo-angiitis obliterans by the fact that it always demonstrates open arterial pulses, is relieved by cold and elevation (which aggravate thrombo-angiitis obliterans) and rarely shows trophic changes.

In the functional disturbances listed as "essential hypertension", dependence is said needed upon the hypertension and the presence of palpable pulses. It must be pointed out that either or both these conditions may be found in thrombo-angiitis obliterans. The functional nature of these disturbances must be demonstrated, but even this does not furnish absolute differentiation since a vasospastic element exists in thirty per cent of cases of thrombo-angiitis obliterans (Allen & Brown, 10-A).

Arteriosclerosis is the condition most frequently requiring differentiation from thrombo-angiitis obliterans. This may be somewhat difficult inasmuch as both diseases share of an organic occlusion. Thrombo-angiitis obliterans occurs in younger individuals in whom the "vis a tergo" and the cardiac power are adequate for compensation and in whom the vascular adaptability is elastic in its



scope. In arteriosclerotic disease, the clinical course is typically milder than in thrombo-angiitis obliterans. When gangrene develops in arteriosclerotic disease the rest type of pain is less severe and the progress is usually slower and more benign than in thrombo-angiitis obliterans. (Brown and Henderson, 11). The presence of diabetes mellitus points to the diagnosis of arteriosclerosis. Radiology may be of possible aid in the demonstration of calcified arteries; arteriographic technic may furnish aid, but argument is not possible, as yet, regarding the differential findings. The characteristics of the arteriogram in thrombo-angiitis obliterans were described above in the section on arteriography. Edwards (37) reported on the arteriographic comparison of thrombo-angiitis obliterans and arteriosclerosis:

Thrombo-angiitis obliterans

- (1) No eccentric filling defects above the site of abrupt occlusion.
- (2) Arteries are less tortuous.
- (3) Fewer collateral arteries.

Arteriosclerosis

- (1) Above the site of abrupt occlusion there are multiple, irregular, eccentric filling defects in the lumen.
- (2) Arteries are more tortuous.
- (3) More collateral arteries.

Edwards pointed out that previous workers had found richer collateral circulation in thrombo-angiitis obliterans than in arteriosclerosis. This seemed reasonable, the author pointed out, on the basis that amputated limbs had been used, rather than those of living patients. The author concluded that the formation of collateral circulation depended upon the duration of the respective processes. On the whole,

arteriography is a very young study and, as yet, furnishes no definite aid, except in obscure cases where the usual, less complicated methods seem inadequate.

In many instances, the diagnosis of arteriosclerosis is made on the age of the patient. It had been pointed out in "Etiology" that at the Mount Sinai (New York) Clinic, when all other factors are equal, those cases below forty-five years of age are considered thrombo-angiitis obliterans, while those above that age are classified as arteriosclerosis — repeating, to be sure, in the sense of a working diagnosis.

In those cases of occlusive arterial disease due to arteritis of known infectious origin, such as rheumatic fever, syphilis, etc., the diagnosis is made upon the history and/or demonstrable evidence of the indicated infection.

Simple thrombosis or embolism may cause occlusive arterial disease. The diagnosis is here made upon the history of causative factors.

Essentially, then, the diagnosis of thrombo-angiitis obliterans is made upon:

(a) History:

The age, sex, and possibly, the race of the patient (Jewish in twenty-eight per cent); the characteristic symptomatology, notable among which is: Intermittent claudication, subjective coldness, the rest pain, aggravation of symptoms by cold, elevation, and exercise.

(b) Findings:

The characteristic color changes of redness in the dependent position, pallor on elevation, evidence of trophic change, absence of osseous change, objective coldness.

The absence of pulsations is valuable only when found; when pulsations are present, the significance is equivocal - due to the fact that certain cases of thrombo-angiitis obliterans show arterial pulsation - so that the diagnosis must be made on the basis of the history and presence of trophic changes.

Oscillometric and arteriographic technics may afford useful aid.

A tabular exposition of the differential diagnosis of the two most important conditions is appended.

COMMON DIAGNOSTIC ERRORS"Flat Feet":

This is probably the commonest diagnostic error, especially when the patient complains of pain in the arches. A moment's consideration shows it can be easily ruled out. In flat feet, the pain in the arches is not relieved by standing still (not walking), while in thrombo-angiitis obliterans, the pain will characteristically leave. Temperature changes, postural color changes and decreased arterial pulses are characteristic of thrombo-angiitis

obliterans and not found in flat feet. Arch supports give no relief in thrombo-angiitis obliterans; the water foot-print test may be of value. The latter should not be too heavily relied upon, however, for many thrombo-angiitis obliterans patients (as well as the general population) may present positive tests yet not be troubled by flat feet.

"Rheumatism" and arthritis are often wrongly considered. The correct diagnosis is ascertained when it is seen that the temperature and postural color changes, as well as arterial pulsations - which show abnormality in thrombo-angiitis obliterans - are normal in the given conditions.

Abnormal or excessive fatigue in the extremities is frequently ignored, or considered part of a general fatigue state. It is important to observe variation in the degree of fatigue in the extremities, as well as coldness, color changes, decreased arterial pulsations, et cetera.

Finally, rubor and rest pain are frequently considered to indicate deep infections of the toes and/or foot, ingrown toe-nails, et cetera. It is very important to avoid this error, for it frequently leads to deep incision which, in the devitalized tissue of thrombo-angiitis obliterans, may well initiate serious gangrene. The diagnosis is easy, usually, and entails little more than quest for the indicated cardinal points.

DIFFERENTIAL DIAGNOSIS OF PERIPHERAL VASCULAR DISEASES (11)

(Modified from Brown and Allen, Buerger and Silbert)

	<u>Thrombo-angiitis obliterans</u>	<u>Arteriosclerosis</u>	<u>Raynaud's Disease</u>
<u>AGE</u>	Chiefly between thirty and fifty years; average forty-two years.	Chiefly after mid-life.	Chiefly between seventeen and thirty-five years.
<u>SEX</u>	Males about ninety-eight per cent.	Males predominate. May be either sex.	Female ninety-five per cent.
<u>RACE</u>	Jews about twenty-eight per cent.	Any.	Any.
<u>REST PAIN</u>	Often very severe.	Usually mild.	Usually absent.
<u>INTERMITTENT CLAUDICATION</u>	Usually present.	Usually present.	Absent.
<u>GENERAL APPEARANCE</u>	Often younger than age.	Often older than age.	Normal.
<u>UPPER EXTREMITIES</u>	Frequently involved.	Seldom involved.	Frequently involved.
<u>POSTURAL CHANGES</u>	Rubor when dependent. Pallor when elevated.	Rubor when dependent. Pallor when elevated.	Absent.
<u>EDEMA</u>	Frequent.	Uncommon.	Absent.
<u>ARTERIES</u>	Pulseless or of diminished volume. Coronary sclerosis rare.	Pulseless or or diminished volume. Coronary sclerosis frequent.	Normal
<u>VEINS</u>	Frequently involved. Often migrating phlebitis.	Rarely involved.	Normal.
<u>ROENTGEN- OGRAMS</u>	Usually negative. Aorta normal.	Frequently calcification of vessels. Possible elongation of aorta.	Normal

## T H E R A P Y

The therapy of thrombo-angiitis obliterans is exceedingly interesting -- not only in view of the pragmatic importance of therapy generally, but also because its study provides an absorbing attempt to thread a maze set up by the trails of many investigators in their efforts to treat a disease of which the etiology is unknown.

It is necessary, before embarking on a study of therapy in thrombo-angiitis obliterans to point out that, inasmuch as the etiology is still unknown, efforts to treat the disease remain on symptomatic and empiric bases. The modern chemist has a better chance, perhaps, to succeed in transmuting metals than his ancestor-chemist - due, admittedly, to his better and more complete understanding of the nature of matter. It is hardly too presumptuous to believe that an analogous situation exists in the field of therapeutics - and specifically, in the present instance. The various forms of therapy will be discussed under two main headings, medical and surgical:

### A. MEDICAL THERAPY

#### 1. Prophylactic Treatment

Inasmuch as the basic etiology of the disease is as yet unknown, experience has demonstrated the existence of predisposing forces of greater or lesser importance. Although it is difficult or impossible

to prognosticate exactly the susceptibility in any given case, Buerger (15) points out that, "In all susceptible individuals..... all the usual stresses of mechanical nature that produce arterial inferiority (excessive exercise, exposure, certain foods, tobacco, etc.) must be avoided." Buerger points out, also, but on more solid ground, that, as soon as the signs of arterial disease are diagnosed, great stress should be laid upon the importance of diminishing the functional demands on the local circulation. Such agencies that are likely to disturb the fine balance between the tissue requirements and the "permanently defective circulation", such as prolonged standing, walking, compressing forces that produce local anemia, such as tight shoes, garters, mechanical insults,-should be scrupulously avoided. It is very important to protect the affected part from the effect of cold, inasmuch as a vasoconstriction may add greatly to the severity in a given case; many cases, especially in the Middle West, seem to be initiated by a case of "frost-bite". (It is wise to visualize the role of the intimal damage in the latter condition.) Woolen stockings are employed advantageously in the prevention of trauma and exposure to cold.

## 2. The Interdiction of Tobacco

The interdiction of the use of tobacco can be hardly over-emphasized. Since early in the history of the disease, its well-nigh invariable association has been repeatedly observed; the reader is referred to the section on Etiology for a resume of the effect of

tobacco upon the blood vascular system. As it would be reasonable to expect, the necessity for the interdiction of tobacco in the treatment of thrombo-angiitis obliterans has been frequently pointed out. To cite a few instances, Willy Meyer (18) in 1925, considered, "The most important therapeutic factor is the stern and absolute interdiction of smoking." Samuels (41) states unequivocally that the use of tobacco must be stopped "immediately and completely." Silbert is one of the staunchest crusaders for the interdiction of tobacco, and he bases his opinion on study of a large series of cases. In 1930, he reported that the cessation of smoking is an essential therapeutic measure, "Most failures can be traced to inability to terminate the habit." In his series, fifty percent of patients who had required amputations had continued to smoke in spite of repeated warnings. He further reported that the recurrence of symptoms, after the individual had been restored to good condition, was almost invariably traceable to the resumption of smoking. He says unequivocally:

"In only two instances, in my experience, has a progression of the disease taken place when the patient was not using tobacco; in one case, an excessive dose of typhoid vaccine given intravenously was followed by immediate closure of a previously open popliteal artery, and in the second instance, prolonged exposure to severe cold was followed by a similar result."

In 1935, we again heard from Silbert, and he reported his experience of ten years with a series of five hundred and twenty-four cases. He speaks in even stronger and more convincing terms regarding the necessity for the interdiction of tobacco:



"In several early cases of thrombo-angiitis obliterans, cessation of smoking without any treatment whatsoever, has resulted in complete disappearance of all symptoms. This regular association of the use of tobacco with the occurrence and the progression of the disease is too striking to be ignored.

"The importance of recognizing the relation between the use of tobacco and the development of thrombo-angiitis obliterans is far from academic. In order to treat patients with this disease successfully, they must be made to stop smoking. It is frequently difficult to induce patients to accept this restriction, but no compromise can be made on this point. Cessation of the use of tobacco is the most important part of the treatment, as this stops the progression of the disease. Efforts to improve the collateral circulation..... are secondary."

From the foregoing, the importance of tobacco and its elimination as an integral part of therapy is strongly pointed out.

### 3. Administration of Fluids

This mode of therapy has an interesting history, and will be found to comprise an important weapon in our therapeutic armamentarium

In 1913, Koga of Japan (quoted in 1) found that the blood viscosity was increased in thrombo-angiitis patients and thus believed the clotting tendency to be increased. This presumably accounted for the formation of thrombotic lesions. With this in mind, Koga, endeavoring to reduce the blood viscosity, gave hypodermoclyses of saline or Ringer's solution in thirteen cases. He is reported as having observed benefit in each instance.

Meyer was impressed by Koga's report, and he tried it in his

own cases, giving hypodermoclyses of 500 c.c. of Ringer's solution every one to three days. He reported <sup>(1)</sup> an excellent result, "...The pain ceased as if by magic."; "The general state became excellent, ulcerations healed, gangrene became localized." This effect was lasting in a minority of the thirty patients treated; the others returned for treatment and benefited thereby. Meyer became very enthusiastic and concluded, "I am ready to say that this treatment deserves a permanent place among the means employed by us in trying to combat thrombo-angiitis obliterans on a conservative basis."

McArthur (4) followed Koga's method and obtained moderate success. He then devised a modified technic of fluid administration; this will be discussed presently. Meleney and Miller (17), in their series in China, attempted the use of intravenous therapy and reported very little success. This report should be evaluated in the light of the investigators' apparent preference for radical therapy (See "Amputation"). Meyer (18) again reported good results with Koga's technic. He used twelve quarts (!) of Ringer's per daily hypodermoclysis in hospitalized patients, with periodic injections for a year after the patient had left the hospital.

McArthur (4) attempted a modification of Koga's technic; he gave Locke's solution per duodenum. He explained his preference by: (1) no local reaction, (2) no difficulty of absorption, (3) a greater volume of fluid could be given, (4) Locke's is a more physiological solution. This method found no appreciable support.

Meyer (1) gave his own modification of Koga's technic. This

concerned the repeated intravenous injection of sodium citrate as a two percent aqueous solution. Sodium citrate was used in view of its use in preventing clotting in indirect transfusions; it was reasoned that it should also prevent intravascular clotting. The results of this modification were favorable at the time, but not conclusive. Ginsburg (5) did not have very satisfactory experience with this method. Steel (9) used this method, giving it to cases over a period of one year, and reported very favorable results. He was very definite and unequivocal in his praise.

In 1926, Silbert published a preliminary report<sup>(22)</sup> on the results of intravenous injection of hypertonic salt solution. He gave two reasons for the use of sodium chloride rather than any of the previous solutions:

- (a) It is the salt to which the body is "accustomed".
- (b) Large quantity (15 grams) can be given without the danger of toxicity.

Silbert gave sodium chloride as a five percent solution in sterile distilled water -- 150 c.c. the first injection, and 300 c.c. for all subsequent injections. "Injections are at first given thrice weekly, later twice weekly -- the length of interval is further increased as the patient improves. The administration of hypertonic salt solution produces a certain amount of blood destruction, but, since the majority of thrombo-angiitis obliterans patients have a high hemoglobin and red cell count, a slight blood destruction is of no serious consequence." No symptoms of anemia were seen, even when treatment had been given for a long time. By the same token, no renal

or cardiac damage was perceived. In a series of sixty-six cases, improvement was obtained in forty-six; unimproved, or too early to judge, fourteen cases; six cases went on to amputation. Improvement was judged by (a) increased warmth (subjective) in extremities, (b) relief of pain, (c) increased temperature in extremities, (d) growth of nails; healing of ulcers (e) appearance of pulsation in previously occluded or collateral vessels. In addition, the injections appeared to render possible successful low amputation.

Silbert's method seemingly supplanted other forms of fluid administration; in 1929 Samuels ( ) reported that it gave the most consistent and beneficial results of all forms of therapy to date. He pointed out the marked lowering of the incidence of amputations necessary under its use.

Four years after his original report, Silbert reported (52) further experience with his method. His original results were corroborated, and, in addition, "... (a) 67% of all patients have either continued to work or returned to work, (b) oscillometer readings improved in 37% of cases, (c) amputations in his cases were between 8% and 9%, while in those cases (histories) not treated by any special method ("untreated") the amputation incidence during the first five years of the disease was 64%." He concluded, "If the patient can be saved from amputation during the first year of treatment, the chances are that such a procedure will never become necessary." Silbert reported his method as entirely safe. Nineteen thousand injections had been given without fatalities or serious reactions. Certain contra-indications exist: (a) age of greater than sixty years, (b) evidence

of cardiac or renal disease, (c) circulatory obstruction due to embolism from cardiac disease or other sources.

In 1935, Silbert reported(101) the results of ten years' experience with his method, with a series of five hundred and twenty-four cases. His results at this time bore firm corroboration of his previous reports (22) and (46). He pointed out, "The percentage of amputations required serves as the best single criterion of the success or failure of a method of treatment for thrombo-angiitis obliterans.... forty cases, or 7.6% of series required amputation, while at the Mayo Clinic, where from 1928-1932, 21.3% required amputation (sympathectomy is supported) at the clinic; Diez (quoted in 101 ) employing ganglionectomy, had 21.8% failures."

Needless to say, Koga's original conception of the rationale of fluid therapy is difficult to accept. Silbert admits that the rationale is not determined, but that the treatment is empiric. He firmly answers Brown and Allen (who say that his results are due to some contaminant causing a non-specific foreign protein reaction) by recording the temperatures of hospital patients. No chills or appreciable temperature reaction were observed. An interesting speculation as to<sup>the</sup> possible mechanism of the therapeutic action of Silbert's method is given in the following: The hypertonic solution increases the osmotic pressure of the blood, which, in turn, causes fluid to pass from the tissues into the blood, increasing the blood volume. The increased blood volume is then postulated to improve the collateral circulation by distending the given vessels. This, it must be remembered,

is at present but an interesting hypothesis.

The value of Silbert's method may be questioned on the basis that the literature is very meager in point of corroboration. It must be remembered, however, that those clinics capable of presenting large series are employed in other lines of therapeutic investigation; witness the Mayo Clinic, where surgery of the sympathetics is being carefully investigated, and those clinics in Cincinnati and Philadelphia, in which the Pavaex treatment is being observed. It must be admitted that favorable results in over five hundred cases cannot be safely ignored.

#### 4. Methods of Application of Heat

It is more or less common knowledge that the application of heat tends to increase local circulation; this was the rationale of this form of therapy until comparatively recently. Lately, when it had been determined that an element of vasospasm exists in many thrombo-angiitis obliterans patients, it was conceived that the heat, by stimulating the parasympathetic nerve-endings, causes a release from the sympathetic vasospasm. Additionally, it is believed that the heat, by the same mechanism, opens up further circulatory channels.

In the early years of the century, strenuous measures were employed; limbs were treated by baking with super-heated air. This was found too heroic, as might well be expected, inasmuch as tissue, to a great extent devitalized, was being treated. The use of sitz baths was then employed to administer heat. Samuels (41) reported the current routine: Twenty to thirty minutes, several times daily, in water heated to a comfortable temperature. He reported that the

vasodilatation so induced was found to be of value. As may be expected, the use of diathermy was attempted and found to give favorable results. The earliest report on the use of diathermy is found in the work of Wright (11).

A further method to provide optimum vascular patency was submitted by Allen and Brown in the form of contrast baths (32). This, however, was frowned upon; Samuels (41) reported that the cold phase may easily result in danger to the precariously balanced vascular state. Allen and Brown advised also the use of carbon filament lamps and other forms of electric light "baths"; they justly advocated caution in the employment of this measure, in view of the danger of causing painful and recalcitrant burns in the diseased tissues.

It should be pointed out that heat is contra-indicated during the active stage of thrombo-angiitis obliterans, and its use should be very cautious in the presence of skin lesions.

In 1923, Goodman and Gottesman<sup>(13)</sup> introduced the use of typhoid vaccine in the therapy of thrombo-angiitis obliterans. They reasoned that, since foreign proteins had given many brilliant results in the treatment of chronic inflammatory conditions, and since thrombo-angiitis obliterans appeared to be a chronic inflammatory disease, favorable results may be expected. They obtained striking relief in all cases treated; and, while admitting that this mode of therapy was used on an empiric basis, it definitely seemed of valuable aid. In 1925, Perla (19), who found little value in the current modes of therapy,

admitted that typhoid vaccine injections might be of aid. In 1927, Brown and Henderson (27) claimed that the injection of foreign protein was valuable in the relief of the continuous type of pain, giving favorable results in eighty percent of cases. In 1928, Allen and Brown summarized their results in the treatment of a series of two hundred cases. This form of therapy was given favorable comment. The method, as then outlined, consisted of the intravenous injection of an original dose of fifteen million to twenty million killed organisms; the injection was repeated four or five times at intervals of three or four days, increasing the size of dose at each injection by a similar number of organisms. "No bad effects had been observed in 6000 injections. After several injections, the reaction may become attenuated, but is returned to original intensity by a 'rest' period of 2 or 3 weeks." Allen and Brown noted a chill and increased temperature of two to four degrees in satisfactory cases. This observation placed the treatment on a reasonable rationale. It is now believed that the basis is a general fever reaction due to <sup>the</sup> injection of a foreign protein. The increased body temperature is believed responsible for a vasodilatation. In the same year, Allen and Smithwick (43) reported a series of thirteen cases in which nine were improved. They reiterated its value and advised that its use be combined with that of other measures; believed "the method described hastens the development of an adequate circulation more effectively than any conservative measures heretofore suggested." In discussing this paper, Straus, of Chicago, and Allen, of Boston, confirmed the



value of the method and urged that it be combined with the use of intravenous fluids. The following year, Samuels reiterated<sup>(41)</sup> the value of this treatment and re-stated the rationale of general fever reaction resulting in vasodilatation. In 1931, however, Samuels (52), discussing the treatment of gangrene in thromboangiitis obliterans, tended to reverse his stand, saying that the action of typhoid vaccine is so short and temporary, and may be attended by sudden large arterial occlusion. As frequently happens in medicine, there is a wave of initial enthusiasm, and it seems that the use of typhoid vaccine is dropping off. Its mention in the more recent literature is sparse.

##### 5. Postural Exercise

Buerger suggested a routine of postural exercises and reported (15) in 1924 that this method gave better results than any other method for enhancing the circulation. The procedure is as follows:

"The affected limb is elevated with the patient lying in bed, to from 60° to 90° above the horizontal, being allowed to rest upon a support for from 30 seconds to 3 minutes, the period of time being the minimum amount of time necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from 2 to 5 minutes, until rubor sets in, the total time being about 1 minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about 3 to 5 minutes, during which time an electric heating pad or hot water bottle is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from 6 to 10 minutes. These cycles are repeated over a period

of 1 hour, some 6 or 7 cycles constituting a seance. The number of seances cannot be categorically stated, but should vary with the case. In a general way, they should occupy 6 to 7 hours a day ..... "....Contraindicated in extensive gangrene, phlegmon, accompanying pain, and recent thrombosis."

This method found warm approbation from Allen and Brown (32), who obtained strikingly beneficial results in their series of two hundred cases. Samuels (52), in 1929, accorded this method the situation of "useful adjuvant", a position it continues to enjoy. Silbert, however, does not employ it to supplement his intravenous saline routine.

#### 6. Passive Vascular Exercise

Recently, there has been developed a mode of therapy employing change of atmospheric pressure in an effort to increase local circulation. In contrast to the postural exercises, the part is maintained at rest; thus is derived the name, "passive vascular exercise." It is erroneously believed by some that this form of therapy represents an entirely new idea. The basic principle is found to stem from work performed over a century ago. Herrmann and Reid (86) give an interesting and accurate resume of the history of the idea.

Sir James Murray, of Dublin, began to work on the idea in 1812, and published a work in 1835 pointing out that the reduction of the pressure upon the body surface "permits the cutaneous vessels easily to fill, and favors the distension, as it were, by suction, while, at the same time, the lungs receive a column of the usual expansive force supporting the interior trunk and organs, pressing

and propelling blood out from the center to the circumference." In 1833, Victor Junod, of Paris, described the use of negative pressure in the treatment of various diseases under the title of "hemospasia" and "Aerotherapeia". In 1835, W. Reid Clanny, of England, working independently, described an apparatus for removing atmospheric pressure from the body or limbs. It was not until 1887 that Edgar Bluck, of England, applied the rhythmic alteration of these pressures "to bring about an influx and efflux of blood in the part or parts affected."

The first record of the use of the principle in the treatment of organic arterial disease was published in 1917 by Sinkowitz and Gottlieb (3), who applied Bier's suction hyperemia in four thrombo-angitis obliterans patients with very good results. In succeeding years, miscellaneous reports confirmed this method as a useful adjuvant.

In 1932, Herrmann designed and built an apparatus that would automatically bring about the rhythmic alternation of the environmental pressure upon an extremity from any desired amount of negative pressure to any amount of positive pressure; the change in pressure was produced inside a glass "boot". Herrmann coined the name "Pavaex" (pa-ssive va-scular ex-ercise) for the treatment. The following year, Hermann and Reid reported a commercially available unit for suction and pressure up to 100 m.m. Hg.. They advised a negative pressure of 80 m.m. and a positive pressure of 20 to 40 m.m., two or more cycles per minute, with a sudden, rapid transition between the types

of pressure. In 1935, Landis and Hitzrot (89) reported their experience with the Pavaex treatment and attempted to detail the rationale. They pointed out that, according to Poiseuille's Law, the amount of fluid flowing through a rigid tube depends upon the fall in pressure along the tube. Thus, Pavaex was advised in cases where the spastic element was absent or minimal; to provide this condition, the uninvolved extremities were given heat. In this series, 80 to 120 m.m. negative pressure for twenty-five seconds and 60 to 80 m.m. positive pressure for five seconds, with a transition period of three seconds; seance of two hours twice daily. After further work, Herrmann and Reid (98) pointed out that the use of the Pavaex "boot" was not without danger; it was contra-indicated when there are signs of acute inflammation, such as superficial phlebitis or intense pain. Beneficial results during the healed stage were reiterated.

The Pavaex method, even so early in its history, is not without critics. Wilson and Roome (103) reported, in May, 1936, lack of benefit in eight cases; they quote De Takats, who, one and one-half years previously, had reported unconvincing results in twenty cases. Allen and Brown, of the Mayo Clinic, and Silbert, of the Mount Sinai Clinic, report<sup>ed</sup> in almost identical words. The former (100), in 1935, said "One thing appears quite certain: The alternate suction and pressure treatment has not produced any results that have not been observed repeatedly as a result of simpler methods....Our own opinion is that good results follow in cases in which good results could be

expected from other measures, and that when good results do not follow other methods, passive vascular exercise is usually valueless." Silbert (110) in February, 1937, gave his tentative opinion on the basis of fifty-two cases. "My impression is that when improvement takes place from this form of treatment (Pavaex) it could have been obtained with simpler methods, and that when other methods fail this method likewise fails."

In April, 1936, Conway attempted to modify the original routine; he employed a gradual, rather than a sudden transition between phases of pressure. He justified this modification on the basis of possible ~~intimal~~ damage by sudden pressure change working on already diseased vessels. His report,<sup>(107)</sup> however, found no benefit in four cases of thrombo-angiitis obliterans.

In February, 1937, Edwards (109) modified the original apparatus by including inside the glass boot an electrical heating unit; he believes this gives maximum vasodilatation that is obviously desirable, especially during the treatment.

In December, 1936, Collens and Wilensky<sup>(108)</sup> reported their latest work on a new method that is called by some "the boot treatment without the boot." Essentially, it is an inflatable cuff applied about the thigh, and inflated and emptied at rhythmic intervals. The rationale is that of a reactive venous hyperemia produced by intermittent venous occlusion, and apparently based upon the work of Lewis and Grant, who, in 1925, demonstrated that this phenomenon seems to give a six hundred percent increase in arterial flow. Collens and

Wilensky obtained excellent results in five cases of thrombo-angiitis obliterans, judged by the relief of pain and rapid healing of ulcers. They employed pressure of 80 to 90 m.m. Hg. in the absence of gangrene and 40 to 50 m.m. where such lesions were present. Obviously, in a technic so very new, it is impossible to find reliable evaluation; this must wait upon further experience. (It should be mentioned that the authors consider this technic as entirely apart from the "suction-pressure" variety of therapy).

#### 7. Irradiation Therapy

It had been pointed out frequently that, in many cases of thrombo-angiitis obliterans, there exists an appreciable degree of vasospasm, and methods of therapy have been based upon the elimination of sympathetic vasoconstriction. It had been reasoned that paralysis of the involved sympathetics by the action of irradiation may accomplish the desired result.

In 1925, Phillips and Tunick<sup>(20)</sup> reported fifty cases of thrombo-angiitis obliterans treated by irradiation over the twelfth dorsal to sacral region inclusive. Excellent results were obtained, as judged by (a) relief of pain, (b) disappearance of venous and lymphatic stasis, (c) improvement of phlebitis, (d) rapid healing of ulcers, (e) improvement in constitutional state.

Ross Golden took up the idea (quoted in 20) and submitted a series of seven cases which substantiated the original result. Finkelshtein (quoted in 20) reported similarly favorable experience and stated that the amputation incidence on his service had been decreased.

Phillips reported eighteen cases, the vast majority of which showed excellent results.

The following year, Beall and Jagoda (24), in Texas, obtained an apparent cure through the use of irradiation. Four years later, in 1930, the same authors reported (49) six cases completely relieved of symptoms after irradiation of the sympathetic ganglia.

In 1935, Pfahler (105) reported on the results of irradiation therapy in thrombo-angiitis obliterans. He quoted French workers, Delherm and Beau, who gave irradiation over the dorso-lumbar and lumbo-sacral regions, while Desplats and Langeron gave irradiation over the suprarenals. Good results were said to have been obtained in both instances.

The literature is lacking in further report on this form of therapy. While the instances can hardly be gainsaid in this work, it is felt that further confirmation is quite desirable.

(The question is put -- Why is irradiation given)  
 (over the sacral region, which supplies para- )  
 (sympathetic innervation? This hardly seems to )  
 (fit into the rationale. )

#### 8. Vasodilator Substances

The use of typhoid vaccine, previously discussed, had been stated to act on a probable basis of vasodilatation resultant from the heat of a fever reaction. Comparatively recently, the use of other vasodilating substances had been attempted; substances that seem to work by virtue of a more direct action upon the vascular tree.

The first mention of this form of therapy in thrombo-angiitis

obliterans is seen in 1927 in the report of Nesselrode (25), who noticed improvement with the use of benzyl benzoate. (Samuels (41), in 1929, summarized the use of vasodilating drugs, such as nitroglycerin and nitrates, as being of doubtful value.)

Interest in the use of tissue extracts began in 1926 when Frey and Kraut isolated, from urine, a substance which caused lowering of the blood pressure upon intravenous administration. Later, Frey found this same action obtainable from the use of fluid from a pancreatic cyst. In 1928, Professor J.S. Schwartzman, of Russia, discovered the therapeutic value of muscle extract in the treatment of angina pectoris; the principle was found to act by producing a central and a local vasodilatation. This work was noted by M.S. Schwartzman, of England, who attempted its use in nine cases of thromboangiitis obliterans; his report in 1931<sup>(51)</sup> submitted favorable results.

In 1935, Barker, Brown and Roth reported (91) on the use, in thirty-five cases of intermittent claudication, of pancreatic extract, myoston (J.S. Schwartzman's muscle extract), and adenosin phosphoric acid and adenosin. In accounting for the favorable results obtained, the authors stated their belief that the mechanism was not one of vasodilatation, but the result of "some direct action upon the contracting ischemic muscles." Six months later, M.S. Schwartzman presented (93) two additional cases of thromboangiitis obliterans improved by treatment with myoston; he contradicted the former workers by asserting the effect was upon a circulatory basis.



In 1936, Rabinowitz (104) reported on his experience with the use of sodium thiosulphate; this was in line with his work on phospholipin metabolism (discussed in "Etiology"). He found that sodium thiosulphate "tends to palliate the deleterious effect of anoxemia in that it exerts a catalytic-like effect by increasing the oxygen absorption in the tissues, thereby aiding in the utilization of available oxygen." He gave sodium iodide thiosulphate in fifty-grain doses every other day for three weeks and twice weekly thereafter for two months. All food rich in phospholipins were eliminated from the diet. Although good results were reported in the form of various manifestations of improved circulation, it goes without saying that more than one report is necessary for the acceptance of a new method of therapeutic attack.

Scupham (83), in 1934, did original work in attempting to produce a therapeutic vasodilatation with the use of theobromine sodium salicylate; he reported favorable results. Newell and Allen (85), in the same year, attempted the use of the same agent. They concluded that this substance will not prove of much value in the therapy of thrombo-angiitis obliterans. They warned against its routine use on the basis of the danger of harmful reactions.

At the present time, a substance known as spasmalgin is being observed for therapeutic value. It contains papaverine, which is known to have a vasodilating action. Reports on its value are not yet at hand, and, although unofficial opinion gives it merit, serious consideration is definitely an affair of the future.

In concluding the consideration of this form of therapy, it

is seen that, although the preponderance of recorded opinion furnishes favorable comment, widespread acceptance must await further and more conclusive experience.

## B. SURGICAL THERAPY

### 1. Arteriovenous Anastomosis

In 1909, in an attempt to circumvent the result of involvement of the arterial tree of the lower extremity, Buerger (A) suggested the production of an arteriovenous aneurysm. His technic described a surgical procedure for the anastomosis of the proximal portion of the femoral artery with the femoral vein - in effect, isolation of the arteries of the limb distal to a point at, or slightly below, Poupart's ligament. The indications advanced were:

- (a) Fairly healthy condition of the femoral artery and vein.
- (b) Patency of the deep veins; patency of the superficial veins - at least of the internal saphenous and its tributaries.
- (c) Absence of extensive local infection with ascending chronic interstitial inflammatory process.
- (d) The suffering of the patient.
- (e) The uselessness of the limb.
- (f) The history of the loss of the other limb.
- (g) Absence of attacks of migrating phlebitis.
- (h) Evidence of arterial occlusion.
- (i) Presence of signs that the limb cannot be saved by other means.

In his review of the methods of therapy up to 1916, Meyer (1) pointed out that arteriovenous anastomosis, although not a

physiological arrangement (reversal of the direction of blood flow), seemed to be valuable where conservative therapy did not help. He admitted that the method was still to be proved in point of ultimate value. The following year, Ginsburg (5) put himself on record as believing that the technic was totally unacceptable; he felt that the impaired circulation were better left alone than manipulated in this fashion.

Jablons (16), in 1925, while speaking against this form of therapy, pointed out the pertinent fact that, in thrombo-angiitis obliterans, the veins are frequently involved -- a point which had been apparently overlooked. With the possibility of the indicated pathology in mind, the author pointed out that the method loses its last vestige of justification. In the same year, Perla (19) unequivocally condemned the method, and, in 1927, was seen the last mention of this therapy; Nesselrode (25) found absolutely no place for it in any plan of treatment.

Ligation of the femoral vein, another relatively early attempt at surgical therapy, was reviewed by Meyer (1). He found some possibility of favorable result and stated that it was still in its trial period (1916). Ginsburg (5), however, found as little value in this method as he did in the case of arteriovenous anastomosis. Perla (19) summed up the parting word for this ill-starred therapeutic attempt, "Ligation of the femoral vein....mentioned only to be condemned as dangerous and unphysiological."

In 1928, Morton and Pearse, Jr.<sup>(39)</sup> reported on the technic of popliteal ligation, a procedure first performed by Oppel. It was pointed out by the authors that it had become established that ligation of a large artery should be accompanied by ligation of its companion vein on the basis of a resultant diminution of gangrene and an increase in functional ability. It had been further shown that indicated ligation resulted in (a) increase in residual arterial pressure, (b) increase in venous pressure, (c) increase in minute volume flow from the end of the divided artery, and (d) an increase in the peripheral arterial circulatory bed. From the foregoing, the authors reasoned that, if, after arterial ligation, gangrene could be prevented by occlusion of the vein, then it might be equally true that impending gangrene from arterial disease could be avoided by vein ligation. Popliteal vein ligation was performed in a series of six cases of thrombo-angiitis obliterans and encouraging results were obtained in the form of (a) increased temperature of skin and muscles, (b) rapid healing of ulcers, (c) return of normal color, (d) relief from pain.

In view of this promising report, it is perhaps strange that the literature is devoid of further mention of this technic. More serious consideration must await additional experience.

These comparatively early surgical attempts at therapy, although admittedly without practical worth, have been included for possible historic value - in an attempt to provide a sense of continuity for the ensuing discussion of more recent methods.

## 2. Nerve Injection

Certain therapeutic methods involved the injection of given nerves. In 1922, Silbert (12) advanced a procedure for the relief of the constant, tormenting, burning pain due to nerve involvement in late cases. Essentially, the method involved the injection of a quantity of absolute alcohol into the exposed nerve. The author pointed out that the possible applicability was limited by the paralysis of important muscles in injecting given parts of the nerve. Silbert reported definite relief from pain in three cases. In 1925, Jablons (16), reviewing the therapy of that time, reported that injection of the posterior tibial nerve with alcohol had not borne out the initial expectations. The same year, Perla (19), analysing his results in a series of forty-one cases, reported, "Injection of 95% alcohol is abandoned by Silbert because the alcohol causes tissue necrosis." This report seems to have concluded the history of this method.

In 1930, Stern (47) gave a preliminary report of a technic for increasing the circulation by the injection with 95% alcohol of the roots of the twelfth thoracic and first and second lumbar nerves. His technic gave favorable results in the form of (a) increased subjective warmth, (b) decreased local cyanosis, (c) filling of collapsed veins when the elevated limb is lowered to the horizontal, (d) no serious paralyses or "any unbearable disturbance of the skin." No further work was seen to corroborate this method. Stern was again heard from. In 1935, he (92) reported on the intra-spinal injection of alcohol and advised that it be done early, before sclerosis pre-

vents the vessels from responding to release from sympathetic innervation. The literature's silence of two years forces the obvious conclusion.

Smithwick and White (48), in 1930, acknowledging Silbert's earlier work, presented a method involving the systematic blocking of all the sensory nerves of the lower leg and foot; this was claimed to be an original modification. The authors pointed out that the anatomical arrangement is very favorable in the leg, for the trunks are widely separated, many are purely sensory, and the mixed nerves "give off no important muscular branches in the inferior two-thirds of the lower leg." The nerves were exposed and injected with 95% alcohol (one to three c.c.); using great care to prevent getting the alcohol into the adjacent tissues. Strict aspesis, of course, was mandatory. The authors reported favorable results in each of eleven patients:

- (a) Relief of pain for a few months or permanently.
- (b) Increased circulation in the foot, judged by rise in skin temperature (as much as 5°) - this was attributed to paralysis of sympathetic fibers in the treated nerves.
- (c) Relief of pain facilitated other therapeutic procedures, such as Dakinization of ulcers, removal of necrotic nails, etc.

Allen treated a series of twenty-nine patients according to this method and reported his results in 1932 (68). Twelve patients went on to major amputation; the remaining seventeen, although most had some surgery (amputation of toes, etc.), were

able to go on with serviceable lower extremities. Allen suggested the value of this method on the basis of these results, but he was not very loud in his approbation. Nothing further has been reported since Allen's article, and if this method is to be taken at all seriously, further work must warrant the recognition.

Following the general idea of peripheral nerve interruption, it is noted that, in 1933, Silbert and Laskey (78) advanced a technic of cutting of the peripheral nerves, after exposing them at given sites in their course down the leg. This work was advanced for the relief of pain; a positive result was obtained in each of eighteen cases. Other features reported as parts of a favorable result were:

(a) Hastening of healing of ulcers: This was considered as possibly obtained by one or both of the mechanisms:

(1) Release of vasoconstriction due to the loss of sympathetic innervation carried in the treated nerves.

(2) Local treatment of the ulcers, such as Dakinization, possibly by virtue of relief from pain.

(b) The operative wound healed easily by primary intention.

(c) No trophic ulcers resulted from the nerve section.

In spite of this very favorable report, the technic was not noticeably attempted by other workers. General acceptance awaits further reports.



### 3. Sympathectomy

Considerable work has been done in various efforts to treat thrombo-angiitis obliterans by surgery directed at the sympathetic nervous system. The basic rationale is an attempt to provide the maximum possible vascularity by eliminating the element of spasm working upon the vessels in the involved part - not only the involved vessels, but also (and perhaps chiefly) in those comprising the collateral circulation.

Perivascular sympathectomy (stripping of the nerves ramifying about the blood vessels) was reportedly advanced by Leriche; statement will be made to justify the necessity for qualifying this assertion. Silbert was apparently the first to assert the lack of value of this method. He pointed out in 1922 (12) that, in view of the work of Potts, who showed (Potts: Anat. Anz. 47:138, 1914) that the sympathetic supply of the large vessels of the lower extremities comes off at various levels along their course from the adjacent nerves, and not through a continuous perivascular sympathetic system, it may be reasonably doubted whether this procedure can be expected to be of value.

Further reports on this technic corroborated Silbert's doubt. Nesselrode, in 1927, (25) affirmed the lack of confidence in the procedure on the basis of an unsatisfactory result in one case. Brown and Rowntree<sup>(32)</sup> (quoted in) reported negative results in the application to seventeen cases. They did not find sufficient justi-

cation to warrant continuation of its use. In 1929, Samuels, reviewing the therapeutic methods to date, found no merit in the technic. In a later report (52), Samuels not only reaffirmed his former stand, but also pointed out the startling news that Leriche himself had warned against the use of <sup>periarterial</sup> sympathectomy in thromboangiitis obliterans. Since that time, this method had been no longer heard from.

A possibly more durable line of investigation is seen in the form of sympathectomy in greater proximity to the spinal cord. Nesselrode, in 1927, gave voice to the suggestion of Kanavel that post-peritoneal ganglionectomy (sympathetic) may be of therapeutic value. In the same year, Brown and Henderson reported (27) a series of eleven cases treated by lumbar ganglionectomy (by Adson). A satisfactory result was obtained in nine cases. It was pointed out that the success of this method rested upon the careful selection of cases; it must be shown that appreciable vasodilatation can occur in the collateral vessels. The authors were not over-sanguine; they warned that the exact status of the technic was to be proved after long periods of post-operative observation.

In 1928, Allen and Brown reported on the results in two hundred cases (32). They found that lumbar ganglionectomy and ramisection produced definite and persistent vasodilatation of the vessels of the feet when vasodilatation is obtainable. The rationale of the therapy was based upon two observations:

- (a) The frequency with which vasoconstriction intermittent disturbances had been observed.
- (b) The quantitative evidence of vasodilatation that occurs in the diseased extremity with increased environmental and body temperatures.

Cases were then classified as to whether or not vasomotor spasm existed in the collateral vessels; operation was advised in those cases that showed evidence of vasospasm. Actually, the cases suitable for sympathectomy were determined by the use of typhoid vaccine injections. It had been pointed out in the section on medical therapy that the injection of typhoid vaccine causes a vasodilatation on the basis of the fever resultant from foreign protein response. A vasomotor index was arrived at in the following manner: Following an injection of typhoid vaccine, the temperatures, oral and skin (leg), were noted at intervals of fifteen minutes during the period of chills and fever. When the skin temperature rose to a higher point than the oral temperature, vasodilatation of the collateral vessels was considered present. The vasomotor index is obtained by substituting the obtained values in the equation:

$$\frac{\text{Increase in surface temperature} - \text{increase in oral temperature}}{\text{Increase in oral temperature}}$$

EQUALS Vasomotor Index.

This indicated the amount of vasodilatation to a given rise in body temperature. Indices in excess of 1.5 were considered favorable for operation. The authors closed on a tentative note, pointing out

that the study was still under investigation, and that the data was, at best, only approximate.

Samuels (52) in 1929, did not share even the tentative enthusiasm. He considered sympathectomy of doubtful and temporary value. However, Robertson (59), in 1932, tended to support the Mayo workers; he reported that, insofar as vasospasm existed, sympathectomy was helpful. He obtained favorable results with its use.

In 1933, Telford and Stopford (69) reported their results in sixteen cases. After having determined the potential vasodilatation by the employment of spinal anesthesia, marked improvement was obtained in nine cases, and moderate benefit in four cases. The authors permitted themselves to go on record as believing that the operation "will prove of value, especially when it is realized that it has the best chance of success in early cases."

Later the same year, Craig, Horton and Sheard (72) reported having found that general anesthesia constituted a satisfactory method for investigating thermal changes in peripheral vascular disease. The vessels of patients who were refractory, or who reacted poorly to other vasodilating agents, were found to undergo maximal dilatation when general anesthesia was administered. The vasodilatation obtained in general anesthesia was found to indicate the maximum response and represented the ideal to be sought in subsequent sympathectomy.

In one case the following year, Stewart (82), of England, "saved" the upper limbs from gangrene by ganglionectomy. He maintained that the posterior approach was better, since a more complete removal was possible than by the anterior approach.

In 1934, the Mayo workers of (32) reversed their stand in (87). They found that fever produced effective vasodilation, while general anesthesia failed in two instances. These workers also modified the technic advanced by Allen and Brown in 1928 (32); this referred to the work done in arriving at the principle of the vasomotor index. Following the work indicated, the rise in surface temperature (vasomotor range) had been studied, and an increase of at least four degrees had been considered as an index for operation. This gave way to a technic in which the maximum surface temperature of the digit most affected was taken as a basis of prediction -- a maximum surface temperature of twenty-nine degrees or higher with fever was regarded as necessary for operation. This work represents the last report of possible significance in the subject of sympathectomy in the therapy of thrombo-angiitis obliterans. The authors' concluding statement is an example of a desirable lack of over-statement:

"It must be kept in mind that thrombo-angiitis obliterans is a relapsing disease. There is no conclusive proof that ganglionectomy prevents recurrence of thrombosis. We believe it decreases the incidence of recurrences, but we have seen several patients in whom recurrences of arterial thrombosis have taken place months after operation. The protective nature of the operation against loss of limbs was demonstrated in these cases."

In terminating the discussion of this mode of therapeutic attack, a modicum of evaluation seems desirable. It cannot be denied that this type of sympathectomy has shown therapeutic value in certain cases, particularly those in which a considerable vasospastic element can be demonstrated. In regard to comparative therapeutic worth, it is appropriate to refer to Silbert's experience of ten years with the use of intravenous hypertonic saline. Silbert (101) pointed out (referred to elsewhere) that while the incidence of amputations under the use of sympathectomy was over twenty-one per cent, with the use of intravenous therapy, the figure was between seven and eight per cent. The significance of these figures forces an obvious conclusion in regard to the matter of present status.

#### 4. Amputation

One of the most regrettable developments in the course of the disease is the necessity for amputation of one or more of the extremities. Quite reasonably, investigative work had been performed with the view of prevention of the distressing result, which has been spoken of in previous sections. However, in instances where amputation becomes necessary, certain considerations must be evaluated - such as, amputation criteria, the site of surgery, et cetera. A review of the work performed is now presented.

In 1925, Meleney and Miller (17), working in China, postulated that the presence or absence of popliteal pulsation<sup>be taken as criterion;</sup> when the popliteal pulse was absent, amputation advised above the knee; when present, amputate below. They felt that, generally, in those cases

where there was "general or local evidence that the collateral circulation can keep pace with or out-run the obliterating process, and the gangrenous area is small, the treatment should be conservative operation. In other cases, the treatment should be radical operation."

Much of the ensuing work was directed at the possibility of keeping the site of amputation below the knee; the importance of this measure, particularly from an economic point of view, can well be seen.

In 1928, Allen and Meyerding (34) reported two indications for amputation: (a) Organic closure of main vessels. (b) Intractable (continuous) pain. These workers refuted the postulated desirability of amputation above the knee; their results showed that amputation below the knee was successful in eighty per cent of cases, provided that adjuvant measures were employed pre- and post-operatively.

In 1928, Allen and Brown (32) contributed from their study of two hundred cases:

"The choice of the area for amputation depends upon the condition of the vascular supply of the extremities. Fingers can usually be successfully amputated regardless of the amount of obliteration in radial or ulnar arteries. Toes can be successfully amputated in only a small group in which the arteries are pulsating normally and the skin proximal to the toes is not discolored or edematous. The study of a large group shows that incision of toes or removal of toe nails is never successful and always necessitates higher amputations. Amputation below the knee is successful

in eighty per cent of cases of thrombo-angiitis obliterans, regardless of the condition of the popliteal artery providing the gangrene does not involve the leg and extensive lymphangitis or edema is not present."

This is at variance with the opinion of other workers who maintain that amputation should always be carried out above the knee. The good result in this series may be due to the pre- and post-operative medical care, consisting of the almost continuous application of heat from carbon filament lamps and intravenous injection of small amounts of foreign protein. Amputation above the knee should be reserved for cases in which amputation below the knee has been unsuccessful and in those in which the patient is unwilling or in poor physical condition to take the risk of a second operation, if amputation at a lower amputation has been unsuccessful.

In 1930, Burke and Meyerding (45) shifted attention to the femoral artery from the previously mentioned popliteal artery. They expressed the opinion that if good pulsation can be felt in the femoral artery 4 cm. or more below the inguinal ligament, the leg can probably be amputated successfully below the knee in a high percentage of cases, even though the popliteal artery is not palpable. They reiterated the value of pre- and post-operative adjuvant therapy.

The following year, Samuels (52) made a strong plea for considerably less frequency of amputation. He stressed the fact that thrombo-angiitis obliterans is often erroneously regarded as progressive and incurable. He outlined a clinical concept of gangrene,



stating that far from every case of thrombo-angiitis obliterans terminates in this form of tissue death. He pointed out that the development of a collateral circulation goes on hand in hand with the pathological process, so that extensive occlusion may exist without the necessary occurrence of gangrene. "As long as the balance between obliteration and development of collateral circulation is maintained, gangrene will not set in. However, gangrene will come on when the balance is thrown off as (a) sudden occlusion of a large artery, (b) use of tobacco, which cuts down the extent of the collateral circulation by its vasoconstrictor action."

Samuels went on to request that "the surgeon must have courage to wait for demarcation of the gangrene..... There have been many unnecessary amputations performed because of the uncontrollable intensity of the pain or because of a mistaken fear that the gangrenous process will spread indefinitely and result in the absorption of harmful toxins." This statement was based on the belief that the pathological process of occlusive arterial disease tended to be one of self-limitation and that self-amputation, following the appearance of a "line of demarcation", occurs, with an appreciable degree of economy. This interesting presentation appealed for the limitation of indications for amputation to:

"(a) Only when the gangrene involves the entire foot, including the heel.

"(b) Pain, per se, is not an indication."

In 1933, McNealy and Shapiro (84) reviewed the criteria for

determination of the site of amputation:

- (a) Level of abrupt temperature change: Limbs are exposed to the air for fifteen minutes, then covered with bed clothing for a similar period. There is a normal gradual acralward decrease in skin temperature; abrupt temperature change at any level indicates vascular occlusion without satisfactory collateral circulation.
  - (b) Oscillometric readings: Not good, except in acute vascular occlusion (Instrument cannot measure the "seeping" non-pulsatile flow).
  - (c) Salt absorption test (McClure-Aldrich intracutaneous salt absorption test): 0.2 c.c. of 0.85% NaCl injected at four inch intervals down the limb. Normally, the wheal remains for sixty minutes; in circulatory deficiency, the absorption-time is markedly reduced. Cannot be used in the presence of inflammatory, static, or nephritic edema.
  - (d) Histamine "flare" test: Depends upon the universal anaphylactoid vasodilatory response, wherever there are capillaries to dilate. 0.1 c.c. of 1:1,000 histamine (in novocaine, to prevent pain) injected intracutaneously at intervals down the limb. Response: At first a cyanotic flush, then, a hyperemic flare, and finally, a wheal. Amputation is done above the level at which the wheal does not appear.
- (Both of the two preceding tests are open to the criticism  
(that they give an index to the skin circulation, but not )  
(necessarily to that of the muscles and bones beneath. )
- (e) Radiology: To determine the condition of osseous structure radio-opaque substances, the use of which had been introduced by Nesselrode (25), are believed too heroic for general use; their effect upon already damaged vessels is not beyond suspicion.

In ninety to ninety-five per cent of cases, simple clinical tests - palpation and oscillometer - were believed sufficient to determine the level of cessation of pulsatile collateral flow. Differentiation

of vasospasm from organic occlusion by: (a) General fever, (b) typhoid vaccine, (c) spinal and general anesthesia, (d) peripheral nerve block, (e) diathermy. Peripheral nerve block is reported as most widely used.

In 1935, Silbert (101) reported, on the basis of ten years' experience with five hundred and twenty-four cases:

- (a) 3.5% of cases inevitably go to amputation, in spite of any treatment.
- (b) Massive gangrene or spreading infection comprise the only reasonable indications for amputation.
- (c) To obtain relief from pain is no indication for amputation; peripheral nerve section will give the desired result.
- (d) Amputation site below the knee, if at all possible -- this, in view of ability to use an artificial limb without a cane, is of great economic importance.

Summarizing the status of amputation to date, certain facts appear to be true:

- (a) The incidence of amputation in thrombo-angiitis obliterans has been reduced, apparently by the use of therapeutic measures, by a considerable margin (see the work of various Mayo Clinic workers and that of Silbert, cited above); some cases inevitably require amputation.
- (b) The optimal amputation site is the most distal point possible.
- (c) The amputation site may usually be determined by means of palpation of susceptible vessels.
- (d) The pre- and post-operative employment of adjuvant measures apparently aid in minimizing the extent of amputation.
- (e) Pain is not necessarily an indication for amputation.

## 5. Adrenalectomy

Adrenalectomy, a mode of therapy advocated practically solely by French workers, has found little of wide acceptance. This method was first employed by Von Oppel in 1921. In 1927, Stulz and Stricker (29) presented a series of eight cases. They concluded, rather equivocally, that their results were sufficiently encouraging to warrant further trial of the method. They admitted that the rationale was not agreed upon. They postulated two possible mechanisms: (a) Changed composition of the blood, (b) release of sympathetic vasospasm dependent upon the role of the adrenal in the autonomic balance.

The following year, Herzberg (quoted in 32) analyzed the results of one hundred and ten cases in which adrenalectomy had been performed. Inasmuch as thirty-two amputations were necessary in the fifty-four cases that had been followed for six months to two years, the report gave scant approbation.

The technic was evaluated in Samuels' review (52) in 1929. This investigator criticized the method on the basis that the remaining adrenal soon makes up for the loss of the opposite gland by secreting a greater quantity of adrenalin. Samuels attempted the use of insulin, advised by the French workers, on the basis that the action of this substance is antagonistic to that of adrenalin. A negative result was reported.

Leriche and Stricker (62) attempted, in 1932, to revive interest in the little accepted method. Their contribution offered favorable results in five cases out of twelve.

Generally, adrenalectomy is considered to have a poor future. At best, it has an up-hill struggle.

#### 6. Local Treatment of Ulcers

A few remarks seem pertinent in the matter of the management of painful ulcers. Buerger (15) advised the use of anesthetic ointments, in addition to the general measures advocated in his work (postural exercises, heat, etc.). Samuels (52) also used anesthetic ointments, after first bathing with chloramine. Silbert, however, pointed out (101) that the use of anesthetic ointments proved deleterious; the ulcerated areas became enlarged and healing was delayed, probably due to induced local ischemia. Consequently, Silbert abandoned these ointments and began to use "desitin" ointment (cod liver oil and Dakin's solution in a bland base) after cleansing with ether; rapid healing was noticed. This worker felt that peripheral nerve section (discussed above) would take care of the pain in a satisfactory manner. Rest of the part in a horizontal or slightly elevated position was quite generally agreed upon.

#### S U M M A R Y

Various attempts have been made in the general effort to advance acceptable treatment for thrombo-angiitis obliterans; these have been discussed and a modicum of evaluation presented. It is appropriate, in summarizing, to draw certain conclusions that seem acceptable:

1. Prophylactic measures, such as outlined by Buerger, are, at least therotically, wise and reasonable.
2. The interdiction of tobacco has been proven a necessary and important measure.
3. The use of intravenous injections of hypertonic saline can hardly be gainsaid; it has given more favorable results than any other method.
4. Sympathectomy (ganglionectomy and ramisection) has given reasonably good results, but remains a major, more or less formidable procedure, not to be performed unless conservative measures fail and in carefully selected cases (demonstrate appreciable vasospastic element).
5. Passive vascular exercise therapy must demonstrate a not as yet proved superiority over simpler measures.
6. Adjuvant measures, such as the various types of heat and postural exercises, are acceptable in supplementing other methods.
7. Measures such as - irradiation (over sympathetic ganglia), vasodilating substances, adrenalectomy, popliteal vein ligation, intermittent venous hyperemia, interruption of peripheral nerves (section and alcohol injection) - have not, as yet, successfully demonstrated sufficient worth to insure widespread acceptance.
8. Certain methods, such as - arteriovenous anastomosis, femoral vein ligation, perivascular sympathectomy, and injection of typhoid vaccine - have fallen by the wayside when they failed to bear out the promise of initial enthusiasm.
9. The use of anesthetic ointments seems ill-advised and may be supplanted by the use of other local agents.
10. Amputation, inevitable, at present, in at least

3.5% of cases, should be performed below the knee unless adequate indication prohibits this site.

11. The evaluation of therapeutic measures must take into consideration that thrombo-angiitis obliterans is a chronic disease, subject to spontaneous remissions and relapses.

NOTE ON PROGNOSIS

Thrombo-angiitis obliterans is a comparatively rare cause of death (See Pathology) and when it does result in exitus, its presence has been long indicated by involvement of the extremities. The main consideration in prognosis is in regard to gangrene; whether the case will require amputation. Previously, the prognosis was regarded as very unfavorable; that most cases eventually lose one or more limbs. Of late, thanks to a better understanding of the phenomenon of gangrene, this point of view is happily undergoing revision. If cases can be observed and treated before the circulation has become seriously compromised -- as judged by trophic lesions, color changes, palpation, thermometry, oscillometry, etc. - the chances of saving the limb are good. Even in many cases that show more than a moderate degree of involvement, the prognosis is good.

Silbert emphasizes that the disease is not necessarily progressive; if noxious factors are removed and efforts are directed toward the improvement of the collateral circulation, the disease is apparently halted and changes indicative of the normal may reappear (such as, return of absent pulsations, increased readings by thermometry and oscillometry, etc.). His incidence of amputations (referred to above) is sufficiently encouraging.



### CONCLUSION

It seems appropriate, at this point, to refer to the introductory remarks prefacing the main body of this work. An attempt has been made to present a comprehensive summary of the present status of the study of thrombo-angiitis obliterans and the past work, which by scientific investigation, has completed the road leading up to the modern concept. It is hoped that the given review has satisfactorily led to a point where it can be said, "Let us start from here."

BIBLIOGRAPHIC NOTE

In the appended section on bibliography, an attempt is made to include a collection of references, which, while not comprising all the literature on the subject, furnishes a representation of the work done in the various phases of the field.

For the convenience of the reader, the bibliography is divided under headings comprising the main sections of the thesis. References are numbered according to their place in the given bibliographic section.

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